Table 7-6. Lung Cancer Exposure-Response Coefficients (K_L) Derived from Various Epidemiological Studies

Fiber Type	Operation	Cohort	EPA (1986) K_L*100	Reference	This Update K_L*100	90% Confidence Interval	Uncertainty Interval[a]	Reference
Chrysotile	Mining and Milling	Quebec mines and mills	0.06	McDonald et al. 1980b	0.029	(0.019, 0.041)	(0.0085, 0.091)	Liddell et al. 1997
			0.17	Nicholson et al. 1979				
		Italian mine and mill	0.081	Piolatto et al. 1990	0.051	(0, 0.57)	(0, 1.1)	Piolatto et al. 1990
	Friction Products	Connecticut plant	0.01	McDonald et al. 1984	0	(0, 0.17)	(0, 0.62)	McDonald et al. 1984
	Cement Manufacture	New Orleans plants			0.25	(0, 0.66)	(0, 1.5)	Hughes et al. 1987
	Textiles	South Carolina plant	2.8	Dement et al. 1983b	2.1	(1.2, 3.4)	(0.81, 5.1)	Dement et al. 1994[b]
			2.5	McDonald et al. 1983a	1	(0.44, 2.5)	(0.22, 4.9)	McDonald 1983a
Crocidolile	Mining and Milling	Wittenoom			0.47	(0.17, 0.87)	(0.084, 1.7)	de Klerk et al. 1994[c]
Amosite	Insulation Manufacture	Patterson, NJ factory	4.3	Seidman 1984	1.1	(0.58, 1.9)	(0.17, 6.6)	Seidman et al. 1986
		Tyler, Texas factory			0.13	(0, 0.6)	(0, 1.8)	Levin et al. 1998
Tremolite	Vermiculite Mines and Mills	Libby, Montana			0.51	(0.11, 2.0)	(0.049, 4.4)	Amandus and Wheeler 1987
					0.39	(0.067, 1.2)	(0.03, 2.8)	McDonald et al. 1986
Mixed	Friction Products	British factory	0.058	Berry and Newhouse 1983	0.058	(0, 0.8)	(0, 1.8)	Berry and Newhouse 1983

Table 7-6. Lung Cancer Exposure-Response Coefficients (K_L) Derived from Various Epidemiological Studies *(continued)*

Fiber Type	Operation	Cohort	EPA (1986) K_L*100	Reference	This Update K_L*100	90% Confidence Interval	Uncertainty Interval[a]	Reference
	Cement Manufacture	Ontario factory	4.8	Finkelstein 1983	0.29	(0, 3.7)	(0, 22)	Finkelstein 1984
		New Orleans plants	0.53	Weill 1979, 1994	0.25	(0, 0.66)	(0, 1.5)	Hughes et al. 1987
		Swedish plant			0.067	(0, 3.6)	(0, 14)	Albin et al. 1990
		Belgium factory			0.0068	(0, 0.21)	(0, 0.84)	Laquet et al. 1980
	Factory workers	US. retirees	0.49	Henderson and Enterline 1979	0.11	(0.041, 0.28)	(0.011, 1.0)	Enterline et al. 1986
	Insulation Application	U.S. insulation workers	0.75	Seilkoff et al. 1979	0.18	(0.065, 0.38)	(0.012, 2.1)	Seilkoff and Seidman 1991
	Textiles	Pennsylvania plant	1.4	McDonald et al. 1983b	1.8	(0.75, 4.5)	(0.2, 16)	McDonald et al. 1983b
		Rochedale plant	1.1	Peto 1980a	0.41	(0.12, 0.87)	(0.046, 2.3)	Peto et al. 1985

[a]Uncertainty Interval formed by combining 90% confidence interval with uncertainty factors in Table A-3.
[b]With supplemental raw data from Terri Schnorr (NIOSH) and Dement
[c]With supplemental unpublished raw data with follow-up through 2001

Among the K_L values derived in the current study, the lowest and highest of the best-estimate values differ by a factor of 300 (excluding the negative study of the Connecticut friction products plant, which would make the spread even larger) and several pairs of uncertainty intervals have no overlap. For example, the K_L uncertainty interval for the chrysotile miners in Quebec lies entirely below the corresponding intervals for chrysotile textile workers (in either of the two studies for South Carolina, which are of highly redundant cohorts in the same plant), for textile workers in the Pennsylvania plant, and for amosite insulation manufacturers (in the Seidman study (1986).

The K_L values and the associated uncertainty intervals are plotted in Figure 7-1. Each exposure environment is plotted along the X-axis of the figure and is labeled with a 4-digit code that indicates fiber type (chrysotile, mixed, crocidolite, or tremolite), industry (mining, friction products, asbestos-cement pipe, textiles, insulation manufacturing, or insulation application); and a 2-digit code indicating the study from which the data were derived. A key is also provided. In Figure 7-1, the chrysotile studies are grouped on the left, amphibole studies are grouped on the right, and mixed studies are in the middle.

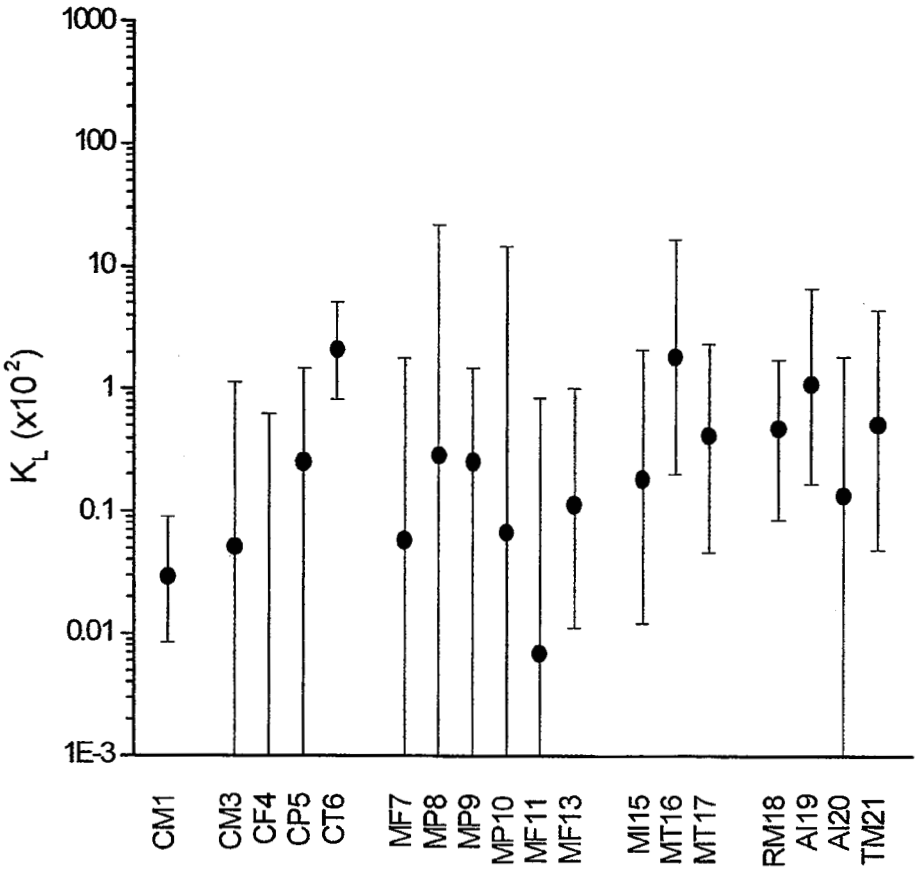
For studies conducted at the same facility (generally among highly overlapping cohorts), such as the Dement et al. (1994) and the McDonald et al. (1983a) studies of the same South Carolina textile facility, a single study was selected for presentation in Figure 7-1. Thus, for South Carolina, the Dement et al. (1994) study is presented because we had access to the raw data for this study. It is also a newer study. Similarly, the Amandus and Wheeler (1987) study was selected to represent the Libby Vermiculite site over the other study at this facility (McDonald et al. 1986). The effects of such selection is expected to be small in any case because the K_L values estimated for the individual studies in each pair vary only by a factor of 2.

Comparisons of K_L values across the available studies are instructive. Within chrysotile studies alone (and excluding the negative friction products study), lowest and highest K_L values vary by approximately a factor of 70. Moreover, as previously indicated, the uncertainty intervals for the lowest (non-zero) value (for Quebec miners) and the highest value (textile workers) have no overlap. Uncertainty intervals for the negative friction product study and the other estimates for chrysotile do overlap, primarily due to the wide confidence interval associated with the negative study.

Among the apparent variations, differences in lung cancer potency observed among Quebec miners versus that observed among South Carolina textile workers has been the subject of much discussion and evaluation, which is worthy of review (Appendix D). The inability to reconcile these differences, appears to be among the biggest obstacles to reliably estimating an overall chrysotile dose-response coefficient for lung cancer.

As indicated in Appendix D, the leading hypothesis for the apparent differences in lung cancer risk per unit of exposure observed between chrysotile mining and textile manufacturing is the relative distribution of fiber sizes found in dusts in these industries. Evidence from several studies indicates that textile workers were exposed to dusts containing substantially greater concentrations of long structures than dusts to which miners were exposed. Thus, the effects of fiber size is considered further in Section 7.4.

Figure 7-1:
Plot of Estimated K_L Values and Associated Uncertainty Intervals by Study Environment



Key for Figures 7-1 through 7-6 Code

Fiber Types (First Digit of Code)	Study Environment (Second Digit of Code)
A = amosite	A = insulation application
C = chrysotile	F = friction products manufacturing
M = mixed fibers	I = insulation manufacturing
R = crocidolite	M = mining
T = tremolite (in vermiculite)	P = ac pipe manufacturing
	T = textile manufacturing
	X = misc. products manufacturing

Study Cohorts
(Last 2 digits)

1 = Quebec miners (Liddell et al. 1997)
2 = Quebec miners (Liddell et al. 1997, raw data)
3 = Italian miners (Piolatto et al. 1990)
4 = Connecticut friction product workers (McDonald et al. 1984)
5 = New Orleans ac pipe manufacturers (Hughes et al. 1987)
6 = South Carolina textile manufacturers (Dement et al. 1994, raw data)
7 = British friction product manufacturers (Berry and Newhouse 1983)
8 = Ontario ac pipe manufacturers (Finkelstein 1984)
9 = New Orleans ac pipe manufacturers (Hughes et al. 1987)
10 = Swedish ac pipe manufacturers (Albin et al. 1990)
11 = Belgium ac pipe manufacturers (Laquet et al. 1980)
13 = Retired factory workers (Enterline et al. 1986)
14 = Factory workers (Liddell et al. 1997)
15 = Insulation appliers (Selikoff and Seidman 1991)
16 = Pennsylvania textile workers (Mcdonald et al. 1983b)
17 = British textile workers (Peto et al. 1985)
18 = Australian crocidolite miners (de Klerk, unpublished, raw data)
19 = New Jersey insulation manufacturers (Seidman et al. 1986)
20 = Texas insulation manufacturers (Levin et al. 1998)
21 = Libby vermiculite miners (Amandus and Wheeler 1987)

Ignoring the negative Connecticut friction products study, the range of K_L values observed across chrysotile studies (70) appears to be substantially narrower than the range observed across all studies (300). However, if the nearly negative study of the Belgium asbestos-cement pipe manufacturers is also removed, the range observed for chrysotile studies is almost identical to the range observed across all studies. This is because the K_L values for Quebec represents the low extreme of both ranges and South Carolina represents the high extreme of both ranges.

Among "pure" amphibole studies, the lowest and highest of the best-estimate K_L values vary by a factor of approximately 9 and the two extremes both derive from within the same industry (amosite insulation). The two studies in question are of amosite insulation manufacturing plants (one in Patterson, New Jersey, and one in Tyler, Texas) that utilized the same equipment (literally) and apparently had similar sources of asbestos (South Africa). Despite the 9-fold difference in K_L values, the uncertainty intervals for these two estimates have substantial overlap. If the arithmetic mean of the values for the two amosite insulation studies is used, K_L values estimated, respectively, for crocidolite mining, amosite insulation manufacture, and mining of vermiculite contaminated with tremolite vary by less than a factor of 2. However, this is possibly fortuitous, given the magnitude of the associated uncertainty intervals (Figure 7-1).

As indicated in Appendix D, for example, it is possible that mining studies tend to exhibit low K_L values relative to studies of asbestos products industries. This is due to the presence of large numbers of cleavage fragments in the dusts that may not contribute to biological activity (because the majority of these may not exhibit the requisite size to be biologically active) but which, nevertheless, are included in estimates of asbestos concentrations in the original epidemiology studies. If the K_L estimates for Libby and Wittenoom could be adjusted for this effect, they might be closer in value to that obtained from the Seidman study.

It is also instructive to compare variation within and between industries. Within industries (especially for a single fiber type), the data are limited. The studies from the two chrysotile mines (Quebec and Italy) show remarkably close agreement, varying by less than a factor of 2. The three studies involving mining of amphibole (Wittenoom and the two studies of Libby) also vary by less than a factor of 2. However, the mean of the amphibole mining group is approximately 10 times the mean of the chrysotile mining group. Moreover, based on inspection of their respective uncertainty intervals, the K_L values for chrysotile mining in Quebec and Crocidolite mining in Wittenoom appear to be incompatible.

Across all asbestos types (including mixed), the asbestos-cement pipe industry shows the greatest variation, including a nearly negative study (best estimate K_L=0.000068) and four more studies with K_L values that range up to 0.0029 producing a variation within this industry of a factor of 40. The friction products industry includes one negative and one positive study. Better agreement is observed among textiles. The two mixed textile plants show K_L values that vary by no more than a factor of 5 from each other and from the K_L for the South Carolina chrysotile textile plant.

7.3 MESOTHELIOMA

The model proposed in the Airborne Health Assessment Update (U.S. EPA 1986) to describe the mortality rate from mesothelioma in relation to asbestos exposure assumes that the mortality rate from asbestos-induced mesothelioma is independent of age at first exposure and increases according to a power of time from onset of exposure, as described in the following relationship:

$$I_M = K_M \cdot f \cdot [(T - 10)^3 - (T - 10 - d)^3] \quad \text{for } T > 10 + d \qquad \text{(Eq. 7-6)}$$

$$= K_M \cdot f \cdot (T - 10)^3 \quad \text{for } 10 + d > T > 10$$

$$= 0 \quad \text{for } 10 > T$$

where:

I_M is the mesothelioma mortality rate at T years from onset of exposure to asbestos for duration d and concentration f;

K_M is the proportionality constant between exposure and mesothelioma response and represents the potency of asbestos;

A more general expression that holds for variable exposure is given by

$$I_M = 3\ K_M \int_0^t f(x)(t - 10 - x)^2 dx \qquad \text{(Eq. 7-7)}$$

where f(x) is the concentration of fibers at time x following the beginning of exposure. This expression reduces to Equation 7-6 when exposure is constant (see Appendix A).

7.3.1 The Adequacy of the Current U.S. EPA Model for Mesothelioma

Access to the raw epidemiology data from a few key studies allowed us to evaluate the adequacy of the U.S. EPA model (Equation 7-6) for describing the time-dependence for mesothelioma in asbestos-exposed cohorts. For this analysis, the raw data from a cohort of chrysotile miners in Quebec was graciously provided by Drs. Douglass Liddell and Corbett McDonald (described in Liddell et al. 1997), the raw data for the cohort of crocidolite miners in Whittenoom, Australia was graciously provided by Dr. Nick de Klerk (unpublished) and the raw data for the cohort of chrysotile textile workers (described by Dement et al. 1994) was graciously provided by Ms. Terri Schnoor of NIOSH and Dr. John Dement of Duke University. The Whittenoom cohort was originally described by Armstrong et al. (1988), but the data provided by Dr. de Klerk included additional follow-up through 1999.

To identify potential effects due to varying statistical procedures, different methods for fitting the U.S. EPA mesothelioma model to epidemiological data were evaluated. In this evaluation, three methods were used to fit the U.S. EPA mesothelioma model to data from Wittenoom.

In the first approach the data were categorized in a manner often available in published form, so this method mimics the method generally used when raw data are not available. The observed mesotheliomas and person-years of observation were categorized by time since first exposure, and the mean exposure level and duration of exposure were calculated for each such category. The U.S. EPA model was then applied to such data using the approach for the typical situation (as described in Appendix A) and results for the Wittenoom cohort are presented in Table 7-7. The K_M value estimated for Wittenoom using this approach is 7.15×10^{-8} (90% CI: 6.27×10^{-8}, 8.11×10^{-8}). The fit of this model to data categorized by time since first exposure is good (p=0.65).

For most of the published epidemiology data sets, the average level and duration of exposure for individual time-since-first-exposure categories are not provided and have to be estimated from cruder data representing cohort-wide averages. Thus for most of the epidemiology data sets, the calculation of K_M is based on cruder information than the calculation presented in Table 7-7.

Table 7-7. Fit of EPA Mesothelioma Model to Observed Mesothelioma Mortality Among Wittenoom, Australia Miners (Deklerk 2001) Categorized by Years Since First Exposure

Years Since First Exposure		Average Duration (years)	Average Concentration (f/ml)	Observed Deaths	Predicted Deaths by Model
Range	Average				
0–5	0	0.643	30.2	0	0.0
5–10	0.19	0.91	30.2	0	0.0
10–15	0.69	0.958	30.0	1	0.6
15–20	1.6	0.970	29.7	5	6.6
20–25	3.3	0.953	29.5	20	17.6
25–30	6.2	0.957	29.3	25	30.1
30–40	11.8	1.05	29.0	90	78.1
40–100	21.5	1.13	28.1	23	31.1
Total				164	164.0
			Goodness of Fit P-value		0.65

Estimates of K_M
$K_M = 7.15 \times 10^{-8}$
90% CI: $(6.27 \times 10^{-8}, 8.11 \times 10^{-8})$

A second approach to fitting the U.S. EPA model to epidemiology data exploits the fact that the mesothelioma model (Equation 7-7) expresses the mesothelioma mortality rate as the product of K_M and an integral involving the exposure pattern, the time of observation, and the 10-year time lag, but not any parameters that require estimation.

The value of this integral was calculated for each year of follow-up of each subject. Person-years of follow-up and mesothelioma deaths were then categorized according to the values of the

integral, and the average value of the integral determined for each category. Results are presented in Table 7-8.

Table 7-8. Fit of EPA Mesothelioma Model to Observed Mesothelioma Mortality Among Wittenoom, Australia Miners (Deklerk 2001) Categorized by Average Value of Integral (Equation 6-12)

Average Value of Integral	Observed Deaths	Predicted Deaths by Model
0	0	0.0
28.4	0	0.0
206.3	1	0.3
732.3	4	1.0
2,038.1	10	2.9
5,153.7	23	6.8
12,385.8	32	13.8
30,639.7	27	25.8
144,801	67	113.3
Total	164	164.0
Goodness of Fit P-value		<0.0001

Estimates of K_M
$K_M=9.00\times10^{-8}$
90% CI: $(7.89\times10^{-8}, 10.2\times10^{-8})$

K_M was estimated by maximum likelihood from Table 7-8 assuming that the observed numbers of cancer deaths in the different categories of the integral were independently Poisson distributed with a mean equal to the mean value of the integral for that category times K_M. The value of K_M obtained in this fashion was $K_M=9.00\times10^{-8}$ (90% CI: 7.89×10^{-8}, 10.2×10^{-8}). This estimate is about 25% larger than obtained with the data categorized by time since first exposure, although confidence intervals obtained from the two procedures overlap. The fit of the model to data categorized by the integral is poor ($p<0.00001$), as the model predicts too few mesotheliomas for small values of the integral and too many mesotheliomas for large values of the integral.

A third method of estimating K_M (termed the "exact method") employs a likelihood that does not involve any categorization of data. With this method, the hazard function, $h(t)=I_M(t)$ and the corresponding survival function (probability of surviving to age t without death from mesothelioma in the absence of competing causes of death), $S(t)=\exp(-\int_0^t h(s)ds)$, are computed for time at the end of follow-up. The contribution to the likelihood of a subject who died of mesothelioma t years after beginning of follow-up is $h(t)*S(t)$, and the contribution of a subject whose follow-up was not terminated by death from mesothelioma is $S(t)$. The complete likelihood is the product of such terms over all members of the cohort. The estimate of K_M

obtained by maximizing the logarithm of this likelihood was $7.95x10^{-8}$ (90% CI: $7.0x10^{-8}$, $9.0x10^{-8}$).

We consider the exact method of computing K_M to be the most accurate and results from this method are reported in the summary table for mesothelioma (Table 7-9, which is a reproduction of Table A-2). The Quebec and South Carolina data sets were thus evaluated using the exact method. However, it is noteworthy that the two other methods described above, one of which is often applied to published data, give similar estimates of K_M, at least for this data set.

The Quebec cohort was subdivided into three subcohorts, believed to correspond to differing amounts of amphibole exposure due to tremolite contamination of the ore at different mining locations, and to use of some imported commercial amphibole at one factory location (Liddell et al. 1997). Location I consisted of workers at the mine at Asbestos where the ore reportedly had less tremolite contamination. Locations 3 and 4 consisted of workers at the large central mine and at smaller mines, respectively, near Thetford, where the ore was more heavily contaminated with tremolite. Location 2 consisted of workers at an asbestos products factory at Asbestos, which processed some commercial amphibole fibers in addition to chrysotile. The exact method of calculating K_M produced the following estimates: Location 1 (8 cases): $K_M=1.3x10^{-10}$ (90% CI: $0.3x10^{-10}$, $4.9x10^{-10}$); Location 2 (5 cases): $K_M=9.2x10^{-10}$, (90% CI: $2.0x10^{-10}$, $35x10^{-10}$); Locations 3 and 4 (22 cases): $K_M=2.1x10^{-10}$ (95% CI: $0.65x10^{-10}$, $6.5x10^{-10}$).

The relative magnitudes of these estimates track with the relative amounts of amphibole exposure estimated for these locations (Liddell et al. 1997), which is consistent with the hypothesis that the mesothelioma risk in this cohort is due, at least in large measure, to exposure to amphiboles.

There were only two confirmed mesothelioma deaths in the South Carolina cohort and four additional suspected deaths. These were too few to permit detailed analysis. Based on both confirmed and suspected mesothelioma deaths, the exact method of analysis gave an estimate of $K_M=0.43x10^{-8}$, 90% CI: ($0.20x10^{-8}$, $0.79x10^{-8}$). Using only the two confirmed mesotheliomas, the same analysis yielded $K_M=0.14x10^{-8}$, 90% CI: ($0.034x10^{-8}$, $0.38x10^{-8}$). Very similar estimates were obtained by estimating K_M from data categorized by time since first exposure and fitting a linear model to the categorized value of the integral in the definition of the U.S. EPA model. Thus, for this cohort comparable K_M values are estimated no matter which of the three methods described above are used for fitting the U.S. EPA mesothelioma model to the epidemiology data.

Table 7-9. Mesothelimoa Exposure-Response Coefficients (K_M) Derived from Various Epidemiological Studies

Fiber Type	Operation	Cohort	EPA (1986) K_M*100	Reference	This Update K_M*100	90% Confidence Interval	Uncertainty Interval[a]	Reference
Chrysotile	Mining and Milling	Asbestos, Quebec			0.013	(0.0068, 0.022)	(0.003, 0.049)	Liddell et al. 1997[b]
		Thedford Mines			0.021	(0.014, 0.029)	(0.0065, 0.065)	Liddell et al. 1997[b]
	Friction Products	Connecticut plant			0	(0, 0.12)	(0, 0.65)	McDonald et al. 1984
	Cement Manufacture	New Orleans plant			0.2	–	(0.033, 1.2)	Hughes et al. 1987
	Textiles	South Carolina plant			0.25	(0.034, 0.79)	(0.023, 1.2)	Dement et al. 1994[c]
					0.088	(0.0093, 0.32)	(0.0025, 1.2)	McDonald et al. 1983a
Crocidolile	Mining and Milling	Wittenoom			7.9	(7, 9)	(3.5, 18)	de Klerk et al. 1994[d]
Amosite	Insulation Manufacture	Patterson, NJ factory	3.2	Seidman 1984	3.9	(2.6, 5.7)	(0.74, 20)	Seidman et al. 1986
Mixed	Cement Manufacture	Ontario factory	12	Finkelstein 1983	18	(13, 24)	(2, 160)	Finkelstein 1984
		New Orleans plant			0.3	–	(0.089, 1)	Hughes et al. 1987
	Factory Workers	Asbestos, Quebec			0.092	(0.04, 0.18)	(0.018, 0.39)	Liddell et al. 1997[b]
	Insulation Application	U.S. insulation workers	1.5	Seilkoff et al. 1979	1.3	(1.2, 1.4)	(0.25, 6.5)	Seilkoff and Seidman 1991
	Textiles	Pennsylvania plant			1.1	(0.76, 1.5)	(0.17, 6.6)	McDonald et al. 1983b
		Rochedale plant	1	Peto 1980; Peto et al. 1982	1.3	(0.74, 2.1)	(0.28, 5.6)	Peto et al. 1985

[a]Uncertainty Interval formed by combining 90% confidence interval with uncertainty factors in Table A-3.
[b]With supplemental raw data from Liddell
[c]With supplemental raw data from Terri Schnorr (NIOSH) with Dement
dWith supplemental unpublished raw data with follow-up through 2001

7.3.1.1 Time Dependence

The U.S. EPA mesothelioma model (Equation 7-6 or 7-7) was next evaluated to determine whether it adequately describes the time-dependence of mesothelioma mortality following cessation of exposure in the Wittenoom and Quebec cohorts. The small number of mesotheliomas observed among the South Carolina cohort precluded a meaningful evaluation of this issue for that cohort.

For times since first exposure longer than 10 years past the end of exposure the mesothelioma model (Equation 7-6) can be rewritten as

$$I_M = 3 * KM * f * d * (t - 10)^2 * \{1 - 3 * [d / (t - 10)] + [d / (t - 10)]^2\} \qquad \text{(Eq. 7-8)}$$

From this expression we see that, when time since first exposure lagged 10 years, (t–10), is large compared to duration of exposure, (d), the model predicts that the mesothelioma mortality rate is approximately proportional to the product of cumulative exposure (the exposure level, f, (f/ml) times the duration of exposure, (d) and the square of time since first exposure lagged 10 years. Thus, the model predicts that the mesothelioma mortality will increase indefinitely with age as the square of time since first exposure lagged 10 years. The availability of raw data from the Wittenoom and Quebec cohorts provides an opportunity to evaluate this assumption.

Table 7-10 shows the fit of the U.S. EPA mesothelioma model to Wittenoom data characterized by time since last exposure, based on the K_M estimated from the exact analysis. There is no indication from this table that the mesothelioma mortality rate declines after the cessation of exposure, or that the model over-predicts the mesothelioma risk at long times after the cessation of exposure. In fact, the model under-predicts the number of deaths at the longest times, as it predicts 76.8 deaths after 30 years from the end of exposure, whereas 96 were observed.

Table 7-11 shows the observed number of mesothelioma deaths in the three separate locations at Quebec, categorized by time since last exposure, and compared with the predicted numbers obtained using the K_M values obtained using the exact fitting method. From all three locations combined the model predicts 10.6 deaths from mesothelioma after more than 30 years following the cessation of exposure, whereas 10 were observed. Although the small numbers of mesotheliomas make it difficult to draw definite conclusions about the adequacy of the model, there is little evidence that the model under or over-predicts the numbers of mesotheliomas at long periods after the end of exposure.

7.3.1.2 Exposure Dependence

The lack of fit of the mesothelioma model (Equations 7-7 and 7-8) to the Wittenoom data categorized by the value of the integral in Equation 7-8 (Table 7-8) suggests that the Wittenoom data may not be consistent with the assumption that the mortality rate is linear in the intensity of exposure (f/ml). Specifically, the mesothelioma model predicts that for fixed time since first exposure and duration of exposure the mesothelioma mortality rate varies linearly with f, the asbestos air concentration. To test this prediction, expected numbers of mesothelioma deaths were calculated for each of four categories of asbestos air concentrations while controlling for

both time since first exposure and duration of exposure.[4] Person-years in the first 10 years following the beginning of exposure were ignored since no mesothelioma deaths occurred in this time interval, as predicted by the model. The relatively few workers who were employed for longer than 5 years were also excluded from this analysis (exposure durations were generally quite short in this cohort, with the average employment duration being <1 year), which means that all follow-up in this analysis occurred after exposure had ended. Results of this analysis are shown in Table 7-12.

Table 7-10. Fit of EPA Mesothelioma Model to Observed Mesothelioma Mortality Among Wittenoom, Australia Miners (Deklerk 2001) Categorized by Years Since Last Exposure

Years Since Last Exposure		Average Value of Integral	Observed Deaths	Predicted Deaths by Model	Observed/ Predicted
Range	Average				
0–1	0.3	35	0	0	0
1–5	3	72	0	0.1	0
5–10	7.5	327	0	0.6	0
10–20	14.9	4025	10	14.4	0.7
20–30	24.7	18058	58	52.9	1.1
30–40	34	39802	79	61.3	1.3
40+	43.6	57952	17	15.5	1.1
30+			96	76.8	1.3
Total			164	144.9	
			Goodness of Fit P-value		0.21

[4]In this analysis the Wittenoom data were categorized by time since first exposure (10–20, 20–30, 30–40, and 40+ years), exposure intensity (0–15, 15–30, 30–60, and 60+ f/ml), and duration of exposure (0–1 and 1+ years). This categorization was facilitated by the facts that in the subcohort being analyzed, exposure had ended prior to the beginning of follow-up, and in the Wittenoom data base exposure intensity was assumed to be constant throughout employment. Within each of the eight [time since first exposure] x [duration of exposure] categories the total number of mesothelioma deaths were allocated to the various exposure intensity sub-categories in proportion to the product of the average exposure intensity times the person-years of observation in each sub-category, thereby producing the expected number of deaths in each sub-category under the assumption that the response was linear in exposure intensity within each [time since first exposure] x [duration of exposure] category, as predicted by the mesothelioma model. These expected deaths and the corresponding numbers of observed deaths were summed across time-since-first-exposure and duration categories to yield observed and expected deaths categorized only by exposure intensity

Table 7-11. Fit of EPA Mesothelioma Model to Observed Mesothelioma Mortality Among Quebec Miners (Liddell 2001) in Each of Three Mining Areas, Categorized by Years Since Last Exposure

Years Since Last Exposure	Average Value of Integral	Person-Years	Observed Deaths	Predicted Deaths by Model	K_M
Location 1					
0–10	94,267.5	77,008	3	3.1	1.34×10^{-10}
10–20	119,190	27,225	2	1.4	
20–30	119,971	22,831	0	1.2	
30–40	181,470	18,321	1	1.4	
40–50	278,118	11,846	2	1.4	
50+	339,160	6,673	0	1.0	
30+			3	3.7	
Total			8	9.3	
Location 2					
0–10	56,377.5	15,065	0	2.5	9.55×10^{-10}
10–20	56,445.7	4,835	2	0.8	
20–30	58,307.7	3,991	0	0.7	
30–40	78,685.8	3,129	2	0.7	
40–50	88,541.2	1,844	0	0.5	
50+	59,590.4	795	1	0.1	
30+			3	1.4	
Total			5	5.4	
Locations 3 and 4					
0–10	194,913	95,299	13	12.7	2.18×10^{-10}
10–20	262,898	23,885	5	4.3	
20–30	179,052	18,777	0	2.3	
30–40	251,766	14,311	0	2.5	
40–50	348,264	8,800	1	2.1	
50+	298,743	4,451	3	0.9	
30+			4	5.5	
Total			22	24.8	

Table 7.12. Comparison of Wittenoom, Australia (DeKlerk 2001) Mesothelioma Deaths to Predicted Deaths Assuming Risk Varies Linearly with Exposure Intensity After Controlling for Years Since First Exposure and Duration of Exposure

Intensity (f/ml)		Mesothelioma Deaths		
Range	Average	Person-Years	Observed	Predicted
0–15	9.7	50,736	32	19.5
15–30	17.0	23,881	51	22.4
30–60	50.3	18,166	27	41.9
>60	100.2	13,353	40	66.3
Total			150	150.0
		Goodness of Fit P-value		<0.0001

Table 7-12 shows that the assumption that the mesothelioma risk varies linearly with exposure intensity leads to a 2-fold under-prediction of risks for exposure intensities below 60 f/ml (83 deaths compared to only 41.8 predicted) and a corresponding over-prediction for exposure intensities above 60 f/ml (only 67 deaths compared to 108.2 predicted). Thus, instead of risk varying linearly with exposure intensity, Table 7-12 indicates that the exposure response is supra-linear, with lower fiber intensities being more potent per f/ml.

7.3.1.3 Discussion of Adequacy of Mesothelioma Model

The mesothelioma model (Equations 7-6 and 7-7) provides adequate fits to each of the three data sets evaluated (Wittenoom, Quebec and South Carolina) when the data are categorized by time since first exposure. The value of K_M estimated from the cohort of crocidolite miners (Wittenoom) was largest and was about 60-fold larger than the K_M estimated from the South Carolina chrysotile textile workers (based only on confirmed mesotheliomas in South Carolina) and more than 100-fold larger than the estimates obtained from the Quebec chrysotile miners who did not work in the factory that utilized crocidolite. This is consistent with numerous indications from the literature that crocidolite is more potent than chrysotile in causing mesothelioma. The relative magnitudes of the K_M for the Quebec data estimated from three locations track with the relative amounts of amphibole exposure estimated for these locations, which is also consistent with the hypothesis that the mesothelioma risk is greater from amphibole exposure than from chrysotile exposure. Despite the very few mesotheliomas in the South Carolina cohort, the K_M estimated from these data is larger than those from Quebec, although the discrepancy is not as large as estimated for lung cancer.

The Wittenoom and Quebec data were evaluated further to see if they were consistent with the prediction of the mesothelioma model that risk continues to increase indefinitely after exposure has ceased. By comparing the observed number of mesothelioma deaths to the number predicted by the mesothelioma model at various times since the cessation of exposure, no evidence was found that mesothelioma risk dropped off below that predicted by the model, at least up to 40 to 50 years after the cessation of exposure. To the contrary, in Wittenoom there was some evidence that the model under-predicted at the longest times since the end of exposure, as past 30 years

from the cessation of exposure there were 96 observed mesothelioma deaths compared to only 76.8 predicted by the model.

Chrysotile is much more soluble than crocidolite and consequently a chrysotile fiber exhibits a much shorter residence time in the body than a comparable-sized crocidolite fiber. Based on *in vitro* studies a chrysotile fiber with a diameter of 1 μm will dissolve in body fluid in approximately 1 year whereas a 1-μm crocidolite fiber will take 60 years to dissolve (see Section 6.2.4). It is noteworthy that despite the short residence time of chrysotile fibers, mesotheliomas deaths have occurred in the Quebec cohort more than 50 years following the cessation of exposure. This suggests that either these mesotheliomas are the result of amphibole contamination of the ore, or else long residence times for inhaled fibers are not necessary for the production of mesotheliomas.

The mesothelioma model predicts that risk is proportional to the intensity of exposure (Equation 7-6) and, at long times past the end of exposure, to cumulative exposure (Equation 7-8). Two analyses of the Wittenoom mesothelioma data suggest that the assumption of a linear exposure-response may not be valid. First, whereas the model is linear in the value of the integral in Equation 7-7, a very poor fit was obtained when the data were categorized according to the value of the integral (Table 7-8). Second, an analysis that categorized the data by intensity of exposure, while controlling for both duration of exposure and time since last exposure, also provided a poor fit (Table 7-12). Both of these analyses exhibit a supra-linear exposure-response in which less intense lower exposures are more potent per f/ml than more intense ones.

In light of these findings, it is interesting that supra-linearity in the exposure-response relationship for lung cancer has also been suggested by fits of data in several studies (see Section 7.2.1.1). Although the effects for lung cancer are difficult to separate from the confounding effects from smoking, common suggestions of supra linearity for both disease endpoints certainly indicate a need to evaluate the nature of the exposure-response models for asbestos in greater detail. This is consistent with the recommendations of the expert panel (Appendix B) that evaluation of a broader range of exposure-response models for mesothelioma is appropriate.

This analysis of the Wittenoom data appear to be one of very few that provide information on the shape of the exposure-response relationship for mesothelioma. It is possible that systematic errors in the exposure data for Wittenoom could have resulted in an apparent supra-linear exposure response. Like most asbestos-exposed cohorts, the estimated exposures for Wittenoom are uncertain. If higher estimated intensities are overestimates, a linear exposure response would appear to be supra-linear, and a linear fit to such data would underestimate the true K_M.

In addition, errors in exposure measurement even if unbiased, can tend to make a linear dose-response appear supra-linear (Crump 2003). Even if the supra-linear exposure response in the Wittenoom data is real, the exposure-response at lower doses is likely to be linear, but with a larger K_M value than was obtained in the fit to the complete data set. If this is the case, our analysis (Table 7-12) suggests that the K_M for the lower exposures is about a factor of two larger than the value estimated from the complete cohort. A factor of 2 is not extremely large compared to the other sources of uncertainty in the analysis. Provisionally, the value of K_M estimated from the complete Wittnoom cohort will be applied in our analysis. In revisions to this

document, it will be important to attempt to evaluate the exposure-response for mesothelioma using data from additional other cohorts.

Given the importance of these two issues: (1) the relative potencies of chrysotile and the amphiboles and (2) the adequacy of U.S. EPA models for predicting the time and exposure dependence of disease, limited analysis of raw data from a small number of additional cohorts is warranted. Recommendations for further research along these lines are discussed in the conclusions to this Chapter (Section 7.6) and parallel the recommendations of the expert panel (Appendix B).

7.3.2 Estimating K_M Values from Published Epidemiology Studies

At the time that the Health Effects Update was published (U.S. EPA 1986), four studies were found to provide suitable quantitative data for estimating a value for K_M and six additional studies provided corroborative support for the mesothelioma model applied. Currently, there are 14 published studies with adequate data for deriving an estimate of K_M (including updates to all four of the quantitative studies evaluated in 1986).

The U.S. EPA mesothelioma model (Equations 7-6 and 7-7) was applied to each of these data sets to obtain study-specific estimates for the mesothelioma dose-response coefficient, K_M. The resulting set of K_M values are presented in Table 7-9. The format for this table is identical to that described in Section 7.2.2 for Table 7-6. As with the K_L values in Table 7-6, the K_M values for all studies presented in Table 7-9 (including those studies that have not been updated since their inclusion in the 1986 Health Effects Update) were re-derived using the modified procedures described in Appendix A. Uncertainty intervals in Table 7-9 for each estimated K_M were derived using the method described in Appendix A.

As Table 7-9 indicates, the K_M values derived in this study and the corresponding values derived in the original 1986 Health Effects Update are in close agreement, none vary by more than a factor of 1.5. Among the K_M values derived in the current study, the lowest and highest of the best-estimate values differ by a factor of approximately 1,400 (excluding the one negative study of Connecticut friction product manufacturers) and many of the pair-wise sets of uncertainty intervals do not overlap. For example, none of the uncertainty intervals for the K_M values derived for any of the environments involving exposure to chrysotile overlap the uncertainty intervals associated with the K_M values derived for either crocidolite mining or asbestos-cement manufacture using mixed fibers at the Ontario plant (Finkelstein 1984). Furthermore, neither of the uncertainty intervals for the K_M values derived for chrysotile mines in Quebec (Asbestos and Thetford) overlap the intervals around K_M values for any of the amphibole environments or any of the mixed environments, except the Quebec factory that is associated with the Asbestos mine (Liddell et al. 1997).

The K_M values and the associated uncertainty bounds derived in the current study are plotted in Figure 7-2. Each exposure environment is plotted along the X-axis of the figure and is labeled with a 4-digit code that indicates fiber type (chrysotile, mixed, crocidolite, or tremolite), industry (mining, friction products, asbestos-cement pipe, textiles, insulation manufacturing, or insulation application); and a 2-digit numeric code indicating the study from which the data were derived.

The key for Figure 7-1 also applies to this figure. In Figure 7-2, the chrysotile studies are grouped on the left, amphibole studies are grouped on the right, and mixed studies are in the middle. As in Figure 7-1, data from the Dement et al. (1994) study are used to represent the South Carolina textile cohort and data from the Amandus and Wheeler (1987) are used to represent the Libby mine cohort in Figure 7-2. Also, the estimated K_M values for the Quebec miners (Liddell raw data) from Asbestos and Thetford Mines, respectively, are averaged in this figure.

Figure 7-2:
Plot of Estimated K_M Values and Associated Uncertainty Intervals by Study Environment

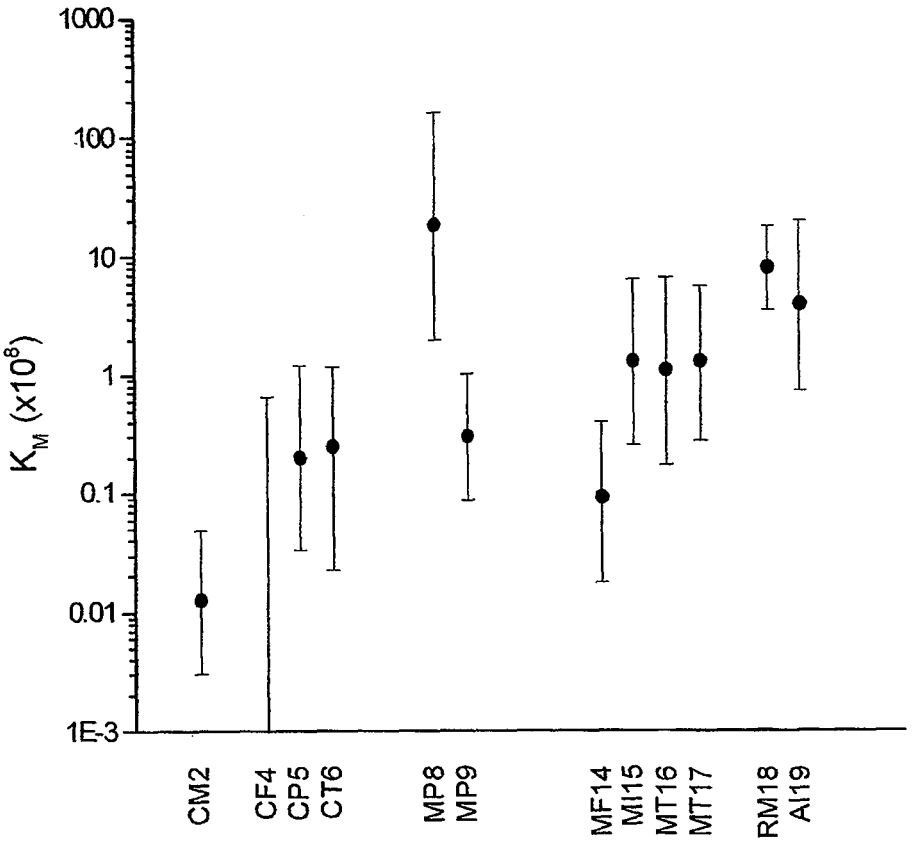


Figure 7-2 indicates that, within chrysotile studies alone, lowest and highest K_M values vary by approximately a factor of 15 (excluding the negative friction products study), which is minimal variation relative to the spread across the values from all of the studies in the table. Also, the corresponding uncertainty intervals have considerable overlap.

The K_M values for the two "pure" amphibole studies (crocidolite mining and amosite manufacturing) agree to within a factor of 2 and, with the exception of the value from the Ontario asbestos-cement plant (MP8 in Figure 7-2 and the ninth study listed in Table 7-9) and the factory plant associated with the Asbestos, Quebec mines (MF14 in Figure 7-2 and the 11th study listed in Table 7-9), the mixed exposure K_M values lie between the high values for the "pure" amphibole exposures and the lower values reported for all of the chrysotile sites. Although the K_M value for the asbestos-cement plant (MP8) appears high, its corresponding uncertainty interval overlaps those of the other "pure" amphibole studies as well as those of a number of the other mixed exposures. The K_M value reported for the factory associated with the Asbestos, Quebec mine (MF14) is the lowest of those reported for mixed exposures, but its uncertainty interval overlaps those for several of the other mixed exposures, as well as all of those involving only chrysotile exposures.

As with K_L values, the asbestos-cement pipe industry shows the greatest variation in K_M values across all asbestos types, with a range of more than a factor of 90. Moreover, the uncertainty intervals for the largest and smallest values in this industry do not overlap. Within the textile industry, the K_M value for the South Carolina chrysotile plant is only an eighth of the values reported for the two textile plants using mixed fibers, although there is considerable overlap in their uncertainty intervals. The potential sources of variation across all of the K_M values are likely attributable to the same sources of variation identified for the K_L values and previously described in detail (Section 7.22).

7.4 EVALUATION OF ASBESTOS EXPOSURE INDICES

As indicated in Chapter 3, for exposure-response coefficients derived from one environment to be applicable in a different environment requires that both of the following two conditions be satisfied:

- that asbestos be measured in both environments in an identical manner; and
- that such measurements reflect (or at least remain proportional to) the characteristics of asbestos exposure that determine biological activity.

When these two conditions are met, it is possible to define an "exposure index" that accurately reflects biological activity, and consequently an exposure-response coefficient based upon such an exposure index derived in one environment can confidently be applied in a different environment. Such an index can be defined as a weighted sum of concentrations of categories of structures of different asbestos types and sizes, where the weights reflect the relative carcinogenic potencies of the different type and size categories. For example, as described in Section 6.4.3, Berman et al. (1995) derived an optimal exposure index from an analysis of rat inhalation studies involving exposures to different types of asbestos and fibrous structures of differing dimensions. The optimum index (defined in Equation 6-11) consists of a weighted sum

of the air concentrations of structures between 5 and 40 μm in length and >40 μm in length (all thinner than 0.4 μm).

There is considerable evidence that the manner in which asbestos is quantified in the available epidemiology studies (i.e., PCM) may not adequately reflect the characteristics that relate to biological activity (Sections 6.4 and 6.5). Therefore, the second of the above two criteria may not be satisfied when exposure-response coefficients (i.e., K_L and K_M values) derived from these studies are used to predict risk in new environments. We therefore investigated the possibility of adjusting the K_L and K_M values so as to apply to a measure of exposure that better reflects biological activity. Such an adjustment requires both (1) data from each studied environment on fiber size and asbestos type needed to adjust the corresponding K_L and K_M and (2) evidence regarding what measure of exposure better reflects biological activity.

7.4.1 Fiber Type and Size Distribution Data Available for Deriving Exposure Indices

Since the range of possible adjustments to the K_L and K_M values is constrained by the data on fiber size and type available from each studied environment, we first consider the characteristics of the data currently available for making such adjustments. The data considered to be pertinent consisted of TEM analyses of samples conducted in the same environment in which an epidemiological study was conducted or from an environment involving a similar operation (e.g., mining, textile manufacture, etc.). Table 7-13 lists available fiber size distributions obtained from a search of the literature and categorized by fiber type and type of operation. The epidemiological studies from which K_L or K_M have been calculated are categorized accordingly.

Assuming that the available TEM size distributions are representative of dust characteristics for the exposure settings (industries) studied, these were paired with corresponding epidemiology studies. The TEM size distributions were then used to convert the exposure measurements used in the epidemiology studies to the new exposure index that potentially better reflects biological activity. Studies were paired as indicated in Table 7-13.

Only a subset of the TEM size distributions listed in Table 7-13 were actually employed in the effort to normalize K_L and K_M values. To minimize variability resulting from differences in TEM analysis methodology employed by different authors, it was decided to employ distributions from common studies conducted by common groups of researchers, to the extent that this could be accomplished without reducing the number of "size-distribution-epidemiological study" pairs available for inclusion in the analysis. Also, studies containing the best documented procedures were favored. Ultimately, with one exception the size distributions selected for use came from only two studies, which were reported in three publications: Dement and Harris (1979), Gibbs and Hwang (1980), and Hwang and Gibbs (1981). In the case of the one exception, size distributions for Libby (tremolite asbestos in vermiculite) were derived from unpublished TEM data recently acquired directly from the site.

Table 7-13. Correlation Between Published Quantitative Epidemiology Studies and Available Tem Fiber Size Distributions

Fiber Type	Exposure Setting	Distribution Reference	Epidemiology Reference
Chrysotile	Textiles	Dement and Harris 1979	Dement et al. 1994, 1983b
		Cherrie et al. 1979	McDonald et al. 1983a,b
			Peto 1980a; Peto et al. 1985
	Friction Products	Dement and Harris 1979	Berry and Newhouse 1983
		Marconi et al. 1984	McDonald et al. 1984
		Winer and Cossett 1979	
		Roberts and Zumwalde 1982	
		Rood and Scott 1989	
	Mining and Milling	Gibbs and Hwang 1980	Liddell et al. 1997
		Winer and Cossett 1979	McDonald et al. 1980b
			Nicholson et al. 1979
			Piolatto et al. 1990
	Asbestos Cement Manufacturing	Dement and Harris 1979	Hughs et al. 1987
		Snyder et al. 1987	
		Winer and Cossett 1979	
Chrysotile and Crocidolite	Asbestos Cement Manufacturing	Hwang and Gibbs 1981	Finkelstein 1984
			Finkelstein 1983
			Hughs et al. 1987
			Weill et al. 1979
			Weill et al. 1994
			Albin et al. 1990
Crocidolite	Mining and Milling	Gibbs and Hwang 1980	Armstrong et al. 1988
		Hwang and Gibbs 1981	de Klerk, unpublished data
Amosite	Insulation Manufacturing	Dement and Harris 1979	Levin et al. 1998
			Seidman et al. 1986
			Seidman 1984
	Insulation Application		Selikoff et al. 1979
	Insulation Clearance	Snyder et al. 1987	
		Cherrie et al. 1979	
Tremolite	Vermiculite Mining	U.S. EPA, unpublished	McDonald et al. 1986
			Amandus and Wheeler 1987

Table 7-14 presents the resulting bivariate fiber size distributions derived from the published TEM data that are paired with representative K_L and K_M values from the corresponding epidemiology studies. This table shows 17 K_L values and 11 K_M values matched with a fiber size distribution from the literature. In this table some length and width categories from some published distributions have been combined, so that, for the most part, only those categories available for all of the epidemiological studies are presented. The column labeled "PCME" ("PCM-equivalent") provides the relative concentrations of asbestos fibers that would have been identified by PCM (≥ 5 μm in length and ≥ 0.2 μm in width).

The fiber size distributions in Table 7-14 are not all of equal relevance to the respective epidemiological studies to which they were paired. As indicated in Table 7-15, some of the distributions are based on data collected at the same facility, others are based on data collected at a similar facility, still others are based on a combination of data from similar facilities, etc. The uncertainty factors listed in Table 7-15 were developed to quantify the relevance of each fiber size distribution to its paired epidemiological study, where larger factors indicate a less certain relevance. How these factors were used is explained below. It should also be kept in mind that, whereas these fiber distributions were based on air samples collected over a fairly narrow time range, they are used to represent the fiber size distributions throughout the exposure period, which in most of the epidemiological studies covers many years.

As indicated in Tables 7-14 and 7-15, for the two environments for which multiple studies were available (i.e., the South Carolina textile plant and the Libby, Montana vermiculite mine), a single study was selected to represent each environment. For the South Carolina textile plant the Dement et al. (1994) study was selected and for Libby, the Amandus and Wheeler (1987) study was selected.

7.4.2 Modification of Existing K_L and K_M to Conform to a New Exposure Index

The fiber size distribution data in Table 7-14 are used to transform the existing K_L and K_M values (which are defined in terms of PCM measurements) so they conform to a different exposure index based on TEM. To see how this is accomplished, consider a K_L value pertaining to a specific environment, let C_{PCM} be an air concentration from that environment measured by PCM, let C_{new} be the concentration in the same air measured by a new exposure index using TEM (e.g., perhaps defined as a weighted sum of TEM concentrations in various length, width and asbestos type categories), and let K_L^* be the adjusted exposure-response coefficient corresponding to the new exposure index. It is clear that for the U.S. EPA lung cancer model (Equation 7-1 or 7-2) to estimate the same risk from the given air concentration using either exposure index, it is necessary that

$$(K_L)\,(C_{PCM}) = (K_L^*)\,(C_{NEW}) \qquad \text{(Eq. 7-9)}$$

Using C_{PCME} (the air concentration of PCM-equivalent fibers - fibers measured by TEM that would be identified by PCM) as a replacement for C_{PCM}, we get

$$K_L^* = K_L\,(C_{PCME} / C_{NEW}) \qquad \text{(Eq. 7-10)}$$

Table 7-14. Representative KL and KM Values Paired with Averaged TEM Fiber Size Distributions From Published Papers

Environment	Study Code	K_L (x100)	K_M (x108)	PCME	Size Distributions															Total			Size Reference	Adjusted	
					w<0.2 L<5	5<L<10	10<L	w<0.3 L<5	5<L<10	10<L	w<0.4 L<5	5<L<10	10<L	w>0.3 L <5	5<L<10	10<L	w>0,4 L <5	5<L<10	10<L	L<5	5<L<10	10<L		K_L (x100)	K_M ($x10^8$)
Quebec mines and mills	CM1	0.029	–	00.14	0.93545	0.00955	0.0023	0.954	0.0113	0.0031	–	0.01322	0.00372	0.0189	0.00915	0.0023	(0.4 Not available in dist)			0.9729	0.02045	0.0054	G&H 1980	0.11	–
Quebec mines	CM2	–	0.0165	0.014	0.93545	0.00955	0.0023	0.954	0.0113	0.0031	–	0.01322	0.00372	0.0189	0.00915	0.0023	(0.4 Not Available in dist)			0.9729	0.02045	0.0054	G&H 1980	–	0.1
Italian mine and mill	CM3	0.051	–	0.014	0.93545	0.00955	0.0023	0.954	0.0113	0.0031	–	0.01322	0.00372	0.0189	0.00915	0.0023	(0.4 Not available in dist)			0.9729	0.02045	0.0054	G&H 1980	0.19	–
Connecticut plant	CF4	0	0	0.07235	0.76359	0.02613	0.01874	0.82804	0.03428	0.02706	0.84938	0.03902	0.03123	0.05473	0.02021	0.03569	0.03339	0.01546	0.03152	0.8877	0.05448	0.06275	D&H 1979	0	0
New Orleans plants	CP5	0.25	0.2	0.05071	0.77469	0.02283	0.01574	0.85992	0.03069	0.02043	0.88663	0.03676	0.02343	0.05080	0.01767	0.02049	0.02408	0.0116	0.01749	0.91072	0.04836	0.04092	D&H 1979	0.54	0.43
South Carolina plant	CT6	1.6	0.17	0.12963	0.65629	0.03024	0.0271	0.74047	0.04333	0.03983	0.7671	0.04959	0.0488	0.07256	0.03921	0.06461	0.04593	0.03294	0.05564	0.81303	0.08253	0.10443	D&H 1979	4.3	0.45
Wittenoom, Australia	RM18	0.47	7.9	0.01167	0.89017	0.02657	0.00503	0.93773	0.03303	0.00617	0.95043	0.0351	0.0063	0.01893	0.00357	0.0005	0.00623	0.0015	0.00037	0.95667	0.0366	0.00667	H&G 1981	0.88	15
Patterson, NJ factory	AI19	1.1	3.9	0.35198	0.17109	0.02872	0.00717	0.30052	0.06018	0.03099	0.37736	0.09111	0.0526	0.31161	0.13463	0.16207	0.23477	0.1037	0.14046	0.61213	0.19481	0.19306	D&H 1979	7	26
Tyler, Texas factory	AI20	0.13	–	0.35198	0.17109	0.02872	0.00717	0.30052	0.06018	0.03099	0.37736	0.09111	0.0526	0.31161	0.13463	0.16207	0.23477	0.1037	0.14046	0.61213	0.19481	0.19306	D&H 1979	0.87	–
Libby, Montana	TM21	0.45	–	4	Not available in distribution							1	1	Not available in distribution									2001 Libby sampling	1.8	–
British factory	MF7	0.058	–	0.07235	0.76359	0.02613	0.01874	0.82804	0.03428	0.02706	0.84938	0.03902	0.03123	0.05473	0.02021	0.03569	0.03339	0.01546	0.03152	0.88277	0.05448	0.06275	D&H 1979	0.13	
Ontario factory	MP8	0.29	18	0.00755	0.93345	0.01125	0.00155	0.95403	0.01378	0.00215	0.9746	0.0163	0.00275	0.02573	0.00298	0.00145	0.00515	0.00045	0.00085	0.97975	0.01675	0.0036	H&G 1981	0.8	49
New Orleans plants	MP9	0.25	0.3	0.00755	0.93345	0.01125	0.00155	0.95403	0.01378	0.00215	0.9746	0.0163	0.00275	0.02573	0.00298	0.00145	0.00515	0.00045	0.00085	0.97975	0.01675	0.0036	H&G 1981	0.7	0.82
Swedish plant	MP10	0.067		0.00755	0.93345	0.01125	0.00155	0.95403	0.01378	0.00215	0.9746	0.0163	0.00275	0.02573	0.00298	0.00145	0.00515	0.00045	0.00085	0.97975	0.01675	0.0036	H&G 1981	0.18	
Belgium factory	MP11	0.01		0.00755	0.93345	0.01125	0.00155	0.95403	0.01378	0.00215	0.9746	0.0163	0.00275	0.02573	0.00298	0.00145	0.00515	0.00045	0.00085	0.97975	0.01675	0.0036	H&G 1981	0.02	
U.S. retirees	MX13	0.11																							
Asbestos, Quebec	MX14		0.092																						
U.S. insulation workers	MI15	0.18	1.3	0.32751	0.1179	0.02183	0	0.27074	0.06114	0.00437	0.34498	0.08734	0.01747	0.37991	0.1441	0.13974	0.30568	0.1179	0.12664	0.65066	0.20524	0.1441	D&H 1979	3.375	24
Pennsylvania plant	MT16	1.8	1.1	0.12963	0.65629	0.03024	0.0271	0.74047	0.04333	0.03983	0.7671	0.04959	0.0488	0.07256	0.03921	0.06461	0.04593	0.03294	0.05564	0.81303	0.08253	0.10443	D&H 1979	4.8	2.9
Rochedale, England plant	MT17	0.41	1.31	0.12963	0.65629	0.03024	0.0271	0.74047	0.04333	0.03983	0.7671	0.04959	0.0488	0.07256	0.03921	0.06461	0.04593	0.03294	0.05564	0.81303	0.08253	0.10443	D&H 1979	1.1	3.5

Table 7-15. Estimated Uncertainty Assigned to Adjustment for Fiber Size

Study Location	Study Code	Estimated Uncertainty Factor	Explanation	KL Reference	KM Reference
Quebec mines and mills	CM1	1	Location common to epidemiology study and size study	Liddell et al. 1997	
Quebec mines	CM2	1	Location common to epidemiology study and size study		Liddell et al. 1997 (raw data Loc. 1,3,4)
Italian mine and mill	CM3	1.75	Same industry, separate locations for epidemiology and size studies	Piolatto et al. 1990	
Connecticut plant	CF4	1.25	Epidemiology location one of several combined for size study	McDonald et al. 1984	McDonald et al. 1984
New Orleans plants	CP5	1.25	Epidemiology location one of several combined for size study	Hughes et al. 1987	Hughes et al. 1987
South Carolina plant	CT6	1.25	Epidemiology location one of several combined for size study	Dement et al. 1994 (raw data)	Dement 2001 (personal communication)
British factory	MF7	1.5	Same industry, separate locations for epidemiology and size studies	Berry and Newhouse 1983	
Ontario factory	MP8	1.5	Epidemiology location probably one of several combined for size study	Finkelstein 1984	Finkelstein 1984
New Orleans plants	MP9	2	Same industry, separate locations, mixed exposures	Hughes et al. 1987	Hughes et al. 1987
Swedish plant	MP10	2	Same industry, separate locations, mixed exposures	Albin et al. 1990	
Belgium factory	MP11	2	Same industry, separate locations, mixed exposures	Laquet et al. 1980	

Table 7-15. Estimated Uncertainty Assigned to Adjustment for Fiber Size *(continued)*

Study Location	Study Code	Estimated Uncertainty Factor	Explanation	KL Reference	KM Reference
U.S. retirees	MX13			Enterline et al. 1986	
Asbestos, Quebec	MX14				Liddell et al. 1997 (raw data)
U.S. insulation workers	MI15	2	Generally similar industries studied for epidemiology and size	Selikoff and Seidman 1991	Selikoff and Seidman 1991
Pennsylvania plant	MT16	2	Same industry, separate locations, mixed exposures	McDonald et al. 1983b	McDonald et al. 1983b
Rochedale, England plant	MT17	2	Same industry, separate locations, mixed exposures	Peto et al. 1985	Peto et al. 1985
Whitenoom, Australia	RM18	1.75	Same industry, separate locations for epidemiology and size studies	DeKlerk, unpublished data	DeKlerk, unpublished data
Patterson, NJ factory	AI19	1.25	Epidemiology location one of several combined for size study	Seidman et al. 1986	Seidman et al. 1986
Tyler, Texas factory	AI20	1.25	Epidemiology location one of several combined for size study	Levin et al. 1998	
Libby, Montana	TM21	1.75	Extrapolated from limited, marginally associated air data	Amandus and Wheeler 1987	

In the actual calculation of K_L*, this equation is applied with the ratio of air concentrations appearing on the right side of this expression replaced by the equivalent ratio of fiber proportions from Table 7-14.

As an example of the calculation of a K_L*, an earlier draft of this report proposed use of an exposure index defined as the weighted sum,

$$0.997\ C_{L>10;W<0.4} + 0.003\ C_{5<L<10;W<0.4} \qquad \text{(Eq. 7-11)}$$

where $C_{L>10;W<0.4}$ is the air concentration of fibers longer than 10 μm and thinner than 0.4 μm, etc. This index is the same as the optimal index derived from animal data (Berman et al. 1995) except the cutoff for the longest length category is 10 μm, rather than 40 μm. To modify, for example, the K_L=0.0029 value from the Quebec mines and mills environment to conform to the exposure index defined by Equation 7-11, we proceed as follows (using the appropriate data from Table 7-14):

$$K_L^* = 0.0029\ [0.014 / (0.003 \cdot 0.013221 + 0.997 \cdot 0.00372)] = 0.0108.$$

K_M* values are derived from K_M values using an identical procedure.

7.4.3 Derivation of an Improved Exposure Index for Asbestos

Based on an evaluation of the broader literature and the results from a series of supplemental studies (Chapter 6), it appears that the asbestos structures that correlate best with biological activity are almost certainly longer and likely thinner than those measured by PCM. As noted above, Berman et al. (1995) found that an exposure index involving only fibers thinner than 0.4 μm, and giving high weight to fibers longer than 40 μm and no weight to fibers shorter than 5 μm, best reconciled data from a collection of studies in rats. Unfortunately, fiber-size distributions available for adjusting epidemiology data (Table 7-14) cover only a fairly limited number of discrete length and width categories. In particular, the largest cut point for fiber length is only 10 μm. This places a severe restriction upon the extent to which the relative potency of fibers of different lengths can be accommodated in an exposure index designed to reflect biological activity.

Although there is evidence that fiber width plays a role in determining potency, the literature suggests that fiber type and length are more important. An earlier draft of this report, which was reviewed by an expert panel (Appendix B), proposed using the exposure index defined by Equation 7-11 for assessing asbestos risk. Panelists agreed that there is a considerably greater lung cancer and mesothelioma risk attributable to fibers longer than 10 μm. However, the panel was uncertain as to an exact cut size for length and the magnitude of the relative potency. They were also uncertain whether the optimal indices for lung cancer and mesothelioma would precisely conform. Some of the panelists recommended determining the specific weighting (i.e., between longer and shorter fibers) that would optimize the fit of the recommended index (Equation 7-11) to the epidemiological studies. That recommendation was followed in this revised document. To address the previously stated concern, the index was optimized separately for lung cancer and for mesothelioma.

In view of the limitations of the fiber distribution data, it was decided, as an interim measure, to adopt a maximum fiber width of 0.4 μm in the proposed exposure index for both lung cancer and mesothelioma. This is the width indicated by the animal data (Berman et al. 1995). Subject to that decision, we then derived separate exposure index indices for lung cancer and mesothelioma, respectively, that are each optimal (as defined below) with respect to fiber type (chrysotile and amphibole) and fiber length (5–10 μm and >10 μm). Based on results of Berman et al. (1995) and lack of compelling evidence elsewhere in the literature (assuming that size effects are adequately addressed, see Chapter 6), it was assumed that all similarly-sized amphibole fibers are equipotent.

To develop separate potency estimates for chrysotile and amphibole fibers (adjusted for fiber size) it was necessary to estimate the relative amounts of chrysotile and amphibole in each environment. Table 7-16 presents our estimates of the fraction of exposure in each study environment contributed by amphibole asbestos, based on information on each environment available in the literature. The source of the information used to develop each estimate as well as a brief description of how the estimate was developed is also provided.

7.4.3.1 Optimizing the Exposure Index for Lung Cancer

A statistical model was fit to the K_L values in Table 7-14 and results from the fitting were used to estimate separate potencies for amphibole and chrysotile, to estimate relative potencies of fibers of different sizes, and to test certain hypotheses. In this model $Ln(K_L)$ (the log transform of a K_L value in Table 7-14) was assumed to be normally distributed with mean equal to

$$Ln\{K_{La}^* \cdot [f_{amph} + rpc \cdot (1 - f_{amph})] \cdot [q \cdot C_{5\text{-}10} + (1 - q) \cdot C_{>10}] / C_{PCME}\} \qquad \text{(Eq. 7-12)}$$

In this expression $C_{5\text{-}10}$ and $C_{>10}$ are the fractions of fibers among those thinner than 0.4 μm that are between 5 and 10 μm in length or longer than 10 μm, respectively (from Table 7-14), C_{PCME} is the fraction of PCME fibers (also from Table 7-14), and f_{amph} is the fraction of amphiboles estimated for each environment (from Table 7-16). In addition there are four parameters that are estimated by fitting the model to the K_L values:

q – the relative potency of fibers thinner than 0.4 μm and between 5 and 10 μm in length, relative to fibers thinner than 0.4 μm and >10 μm in length;

K_{La}^* – the potency (K_L value) of pure amphibole (based upon the exposure index defined by q);

rpc – the relative potency of chrysotile, relative to amphibole

The fourth parameter, σ, is described below.

Note that the part of Equation 7-12 that is inside the curly brackets is like Equation 7-9 solved for K_L but with an additional term to account for the relative amounts of chrysotile and amphibole.

Table 7-16. Estimated Fraction of Amphiboles in Asbestos Dusts

Study Location	Study Code	Fraction of Amphiboles: Best Estimate (%)	Fraction of Amphiboles: Estimated Range (%)	Source of Estimate	KL Reference	KM reference
Quebec mines and mills	CM1	1	0–4	Sebastien et al. 1986, extrapolated from air data	Liddell et al. 1997	
Quebec mines	CM2	1	0–4	Sebastien et al. 1986, extrapolated from air data		Liddell et al. 1997 (aw data Loc. 1,3,4)
Italian mine and mill	CM3	0.3	0.1–0.5		Piolatto et al. 1990	
Connecticut plant	CF4	0.5	0–2	McDonald et al. 1984, extrapolated from plant history	McDonald et al. 1984	McDonald et al. 1984
New Orleans plants	CP5	1	0–2	Hughs et al. 1987, extrapolated from plant history.	Hughes et al. 1987	Hughes et al. 1987
South Carolina plant	CT6	0.5	0–2	Sebastien et al. 1989 (based on), extrapolated from Quebec source material	Dement et al. 1994 (raw data)	Dement 2001 (personal communication)
British factory	MF7	0.5	0–2	Berry and Newhouse 1983, extrapolated from plant history	Berry and Newhouse 1983	
Ontario factory	MP8	30	10–50	Finkelstein 1984, extrapolated from plant history	Finkelstein 1984	Finkelstein 1984
New Orleans plants	MP9	5	2–15	Hughes et al. 1987, extrapolated from plant history	Hughes et al. 1987	Hughes et al. 1987
Swedish plant	MP10	3	0–6	Albin et al. 1990, extrapolated from plant history	Albin et al. 1990	

Table 7-16. Estimated Fraction of Amphiboles in Asbestos Dusts *(continued)*

Study Location	Study Code	Fraction of Amphiboles: Best Estimate (%)	Fraction of Amphiboles: Estimated Range (%)	Source of Estimate	KL Reference	KM reference
Belgium factory	MF11				Laquet et al. 1980	
U.S. retirees	MX13				Enterline et al. 1986	
Asbestos, Quebec	MX14					Liddell et al. 1997 (raw data)
U.S. insulation workers	MI15	50	25–75	Guess estimate for broad industry	Selikoff and Seidman 1991	Selikoff and Seidman 1991
Pennsylvania plant	MT16	8	3–15	McDonald et al. 1983b, extrapolated from plant history	McDonald et al. 1983b	McDonald et al. 1983b
Rochedale, England plant	MT17	5	2.5–15	Peto et al. 1985, extrapolated from plant history	Peto et al. 1985	Peto et al. 1985
Whitenoom, Australia	RM18	97	95–100	General estimate[a]	DeKlerk, unpublished data	DeKlerk, unpublished data
Patterson, NJ factory	AI19	97	95–100	General estimate[a]	Seidman et al. 1986	Seidman et al. 1986
Tyler, Texas factory	AI20	97	95–100	General estimate[a]	Levin et al. 1998	
Libby, Montana	TM21	95	90–100	General estimate[a]	Amandus and Wheeler 1987	

[a]Allows for the possibility of some foreign material. Practical effect for the analysis is nil. Might just as well assume 100%.

With this formalism, the potency, K_{Lc}*, of pure chrysotile is defined by the product, rpc . K_{La}*. Thus rpc=1 corresponds to equal potency of amphibole and chrysotile and rpc=0 corresponds to chrysotile being non-potent for causing lung cancer. Similarly, q=1 corresponds to fibers between 5 and 10 μm in length having the same potency as fibers longer than 10 μm and q=0 corresponds to such fibers being non-potent for causing lung cancer.

The variance of Ln(K_L) was assumed to be composed of two components. The first component, σ_i, was calculated so as to reflect the uncertainty in the K_L values as reflected by both the uncertainty intervals reported in Table 7-6 and the uncertainty in the relevance of the size distributions applied to each environment, as reported in Table 7-15. Specifically, the upper bound of the uncertainty interval for K_L in Table 7-6 was modified by multiplying it by the uncertainty factor in Table 7-15. This modified upper bound was then divided by the best estimate of K_L from Table 7-6, and then divided by 2.0. The log transform of the result was defined as σ_i. A second component, σ, of the standard deviation, assumed to be constant for all studies, was also estimated. This component may be thought of as representing the uncertainty in the K_L estimate resulting from random variation that is not represented in the σ_i. The overall standard deviation of the Ln(K_L) from the study was assumed to be $(\sigma_i^2+\sigma^2)^{1/2}$.

Using the model described by Equation 7-12, parameters (q, K_{La}*, rpc, and σ) were estimated by maximum likelihood and likelihood tests were used to test the hypotheses that chrysotile was non-potent (rpc=0) or equally potent (rpc=1) with amphibole (Wilks 1963). Results from the analysis are summarized in Table 7-17. Shaded values in the table indicate parameter values that were fixed rather than estimated for each particular model run. By holding certain parameters fixed, we evaluated the fit of a range of exposure indices, defined as indicated. This table also contains results from a similar analysis of mesothelioma dose-response coefficients (K_M), which are discussed in Section 7.4.3.2.

The results of fitting the model defined by Equation 7-12 to the K_L values in Table 7-14 are shown in the columns of Table 7-17 labeled "Equation 7-12". The first column, labeled "optimized values" contains the resulting parameter estimates and log-likelihood with all four parameters estimated. Note that the estimate of q is q=0. Since q represents the potency of fibers between 5 and 10 μm in length, relative to fibers >10 μm in length (considering only fibers thinner than 0.4 μm), the model predicts that fibers between 5 and 10 μm are non-potent in causing lung cancer.

The estimate of rpc for the optimized model run of Equation 7-12 is rpc=0.266, which predicts that chrysotile is about 25% as potent as amphibole in causing lung cancer (after adjusting for fiber size). The fourth and fifth columns of Table 7-17 contain results of fitting the model with rpc fixed at either rpc=0 or rpc=1 (both with q fixed at q=0). These results are used to conduct likelihood ratio tests of the hypotheses that rpc=0 and rpc=1. The resulting test for rpc=0 is highly significant (p=0.007). Thus, with this formulation the hypothesis that chrysotile is non-potent in causing lung cancer can be rejected. The test for rpc=1 is non-significant (p=0.54),indicating that even though the best estimate is that chrysotile is only one-fourth as potent in causing lung cancer as amphibole, the hypothesis that chrysotile and amphibole are equally potent cannot be rejected.

Table 7-17. Results from Fitting Exposure Indices Defined by Equation 7.12 and Pcme to Lung Cancer and Mesothelioma Exposure-response Coefficients Estimated from Different Environments

Variable	Index Defined by Equation 7.11	Equation 7.12			PCME		
		Optimized Values	RPC=1	RPC=0	Optimized Values	RPC=1	RPC=0
			Lung Cancer (N=16)				
RPC	0.267	0.266	1	0	0.469	1	0
$100*(K_{LA})$	2.3	2.34	0.953	15.80	0.48	0.29	4.42
s	1.007	1.004	1.092	1.730	1.050	1.070	1.915
Log-likelihood	-17.1022	-17.0833	-17.2659	-20.6989	-17.3451	-17.6271	-21.8543
q	0.003	0	0	0	NA	NA	NA
Hypothesis tests			H_0: RPC=1 p=0.20	H_0: RPC=0 p=0.001		H_0: RPC=1 p=0.54	H_0: RPC=0 p=0.007
$100*(K_{LC})$	0.61	0.61	0.953	0	0.23	0.29	0
			Mesothelioma (N=11)				
RPC	0.0013	0.0013	1	0	0.0033	1	0
$10^8*(K_{MA})$	26.78	26.99	2.54	28.8	7.69	0.737	8.87
s	0.6062	0.6038	1.903	0.6099	0.7605	1.805	0.7782
Log-likelihood	-9.33248	-9.31812	-16.7403	-9.35267	-10.4599	-16.16	-10.5931
q	0.003	0	0	0	NA	NA	NA
Hypothesis tests			H_0: RPC=1 p=0.0007	H_0: RPC=0 p=0.61		H_0: RPC=1 p=0.0001	H_0: RPC=0 p=0.79
$10^8*K_{MC})$	0.035	0.035	2.54	0	0.025	0.74	0

Notes: Shaded areas indicate values that were fixed in advance of the analyses.

"NA" means not applicable.

Also shown in Table 7-17 are the results of applying the exposure index proposed in the earlier draft of this report (Equation 7-11). This index assigns a small relative potency of 0.003 to fibers between 5 and 10 μm in length, compared to the fully optimized model, which, as noted above, assigns zero potency to these fibers. Table 7-17 indicates that both the quality of fit (by comparison of likelihoods) and the resulting parameter estimates are virtually identical. Accordingly, unless the ratio of fibers between 5 and 10 μm in length to those longer than 10 μm (among those thinner than 0.4 μm) in an environment is extremely large (e.g., >300-fold), the two indices will provide practically equivalent results.

As previously indicated, the current approach for estimating asbestos-related risk (U.S. EPA 1986) uses (effectively) PCME as the exposure index. To allow comparison with this approach, analyses were also conducted using PCME as the exposure index, rather than the size range of fibers considered heretofore (i.e., Equation 7-12 was simplified to $Ln\{K_{La}^* \cdot [f_{amph} + rpc \cdot (1 - f_{amph})]\}$). Results of this analysis are shown on the right side of Table 7-17. With this exposure index, the best estimate is that chrysotile is about one-half as potent as amphibole, the hypothesis that chrysotile is non-potent can be rejected ($\bar{p}$=0.001), and the hypothesis that chrysotile and amphibole are equally potent cannot be rejected (p=0.20).

Based upon a comparison of either the residual variance, σ, or the likelihood, it appears that the exposure index defined by fibers longer than 10 μm and thinner than 0.4 μm (corresponding to q=0 in Table 7-17) provides at most a very marginal improvement in fit over use of PCME as the exposure index for lung cancer when rpc is held at 1. Similarly, adjusting for fiber type but not size (i.e., optimizing rpc to reflect separate potencies for chrysotile and the amphiboles) also provides at best a marginal improvement over the current approach (PCME with rpc=1). However, when the exposure index is adjusted for both fiber size and type, (comparing the optimized values for Equation 7-12 to PCME with rpc=1), a small improvement is apparent. The log-likelihood increases by half a unit and the spread in the estimated K_L values (represented by σ) decreases by about 7%. Moreover, as discussed in the following section, the improvement for mesothelioma is substantial..

In addition to the analyses reported in Table 7-17, other analyses were conducted in which an additional term was added to the linear combination of fiber lengths appearing in Equation 7-12 to represent fibers shorter than 5 μm (still considering only fibers thinner than 0.4 μm). In this analysis, the best estimate of both the potencies of fibers shorter than 5 μm, and between 5 and 10 μm in length, was zero.

Discussion of the results from the analysis of the mesothelioma values (also presented in Table 7-17) is provided in Section 7.4.3.2. Based on this analysis and the rest of the evaluation described in this chapter, a recommended set of lung cancer and mesothelioma exposure-response coefficients is presented in Section 7.5.

7.4.3.2 Optimizing the Exposure Index for Mesothelioma

Concomitant with the analysis reported in Section 7.4.3.1 regarding development and evaluation of an improved exposure index for lung cancer exposure-response coefficients (K_L values) that correlates better with biological activity, a parallel analysis was performed for the mesothelioma exposure-response coefficients (K_M values) presented in Table 7-14. This table presents data from 11 environments in which K_M values are paired with fiber size distribution data. The corresponding uncertainty intervals for these 11 K_M values are provided in Table 7-9. The same relationship defined by Equation 7-9 was used to adjust these K_M values to a different exposure index and the same statistical model (Equation 7-12) was applied both to evaluate different adjustments and to develop an adjustment that was optimal for the available data. The results of this analysis of K_M values are presented in the bottom half of Table 7-17, which also contains the results of the comparable analysis of K_L values.

The results of fitting the model defined by Equation 7-12 to the K_M values in Table 7-14 are shown in the columns of Table 7-17 labeled "Equation 7-12". The first of these columns, labeled "optimized values" contains the resulting parameter estimates and log-likelihood with all four parameters estimated. Just as was the case with the analysis of K_L values, the best estimate of q is q=0. Since q represents the potency of fibers between 5 and 10 μm in length, relative to fibers >10 μm in length (considering only fibers thinner than 0.4 μm), just as was the case for lung cancer, the model predicts that fibers between 5 and 10 μm are non-potent in causing mesothelioma.

For mesothelioma, the best estimate of rpc is rpc=0.0013, which predicts that chrysotile is only 0.13% as potent as amphibole in causing mesothelioma (after adjusting for fiber size). This small estimate for rpc is not significantly different from rpc=0 (p=0.79). Consequently, in this analysis, the data are consistent with the hypothesis that all of the mesotheliomas occurring in cohorts exposed primarily to chrysotile are due to small amounts of amphibole contamination within the chrysotile. Moreover, the hypothesis that chrysotile and amphibole are equally potent in causing mesothelioma (the assumption inherent in the U.S. EPA (1986) asbestos health effect document) is clearly rejected (p=0.0001).

Results using PCME as the exposure index for mesothelioma (the bottom right side of Table 7-17) are similar. The best estimate is that chrysotile is only 0.0033 as potent as amphibole, the hypothesis that chrysotile is non-potent cannot be rejected (p=0.61), and the hypothesis that chrysotile and amphibole are equally potent is definitely rejected (p=0.0007).

Based upon a comparison of either the residual variance, σ, or the likelihood, it appears that the exposure index defined by fibers longer than 10 μm and thinner than 0.4 μm (corresponding to q=0 in Table 7-17) provides an improvement in fit over use of PCME as the exposure index for mesothelioma. Even after adjusting for the effects of fiber type (i.e., comparing the σ values estimated for the optimized values with PCME and Equation 7-12 as the exposure index, respectively), the variation across K_M values appears to decrease by more than 20% when values are adjusted to the index of fibers that are longer than 10 μm and thinner than 0.4 μm. Moreover, comparing σ values between the index in current use (PCME with rpc=1) (U.S. EPA 1986) and the optimized index of longer and thinner fibers (with rpc=0.0013), use of the latter exposure index results in a 67% reduction in variation across K_M values.

As was also the case for the lung cancer analysis, the fit based on the exposure index defined by Equation 7-11, which was proposed in an earlier version of this report (with q, the relative potency of fibers between 5 and 10 μm compared to fibers longer than 10 μm fixed at q=0.003), is virtually identical to the fully optimized fit (which predicts q=0).

In addition to the analyses reported in Table 7-17, another analysis for mesothelioma were conducted in which an additional term was added to the linear combination of fiber lengths appearing in Equation 7-12 to represent fibers shorter than 5 μm (still considering only fibers thinner than 0.4 μm). In this analysis, the best estimate of the potency of fibers shorter than 5 μm was also zero.

Based on results in this section and the corresponding evaluation of lung cancer (Section 6.4.3.1) a recommended set of lung cancer (and mesothelioma) exposure-response coefficients are developed and presented in Section 7.5.

7.5 THE OPTIMAL EXPOSURE INDEX

7.5.1 Definition of the Optimal Index and the Corresponding Exposure-Response Factors

Table 7-17 presents the results of fitting a statistical model to asbestos exposure-response coefficients to estimate the relative potencies for fibers of various sizes and types that define an optimized exposure index for asbestos. Although the coefficients for lung cancer (the K_L values) and mesothelioma (the K_M values) were separately evaluated, the optimal index for each incorporates the same size range of fibers (at least based on the limited range of options evaluated). These are fibers longer than 10 μm and thinner than 0.4 μm.

Results in Table 7-17 also differentiate between the potency of chrysotile and amphibole for both lung cancer and mesothelioma. Amphibole is estimated as being about four times as potent as chrysotile for lung cancer (although the difference is not significant) and about 800 times as potent as chrysotile for mesothelioma (a highly significant difference). Moreover, the data are consistent with the hypothesis that chrysotile has zero potency toward the induction of mesothelioma.

The optimized dose-response coefficients (rounded up) from Table 7-17 for pure fiber types (chrysotile or amphibole) are summarized in Table 7-18. These coefficients apply to exposures quantified in terms of concentrations (in f/ml) of fibers longer than 10 μm and thinner than 0.4 μm.

Table 7-18. Optimized Dose-Response Coefficients for Pure Fiber Types

Fiber Type	$K_{L^*} \times 100$	$K_{M^*} \times 10^8$
Chrysotile	0.6	0.04
Amphiboles	3	30

7.5.2 Evaluation of the Optimal Exposure Index

The optimal coefficients presented in Table 7-18, result from adjustments for both fiber type and fiber size to the K_L and K_M values obtained directly from the literature (Tables 7-6 and 7-9), which are linked to PCM measurements. To get some idea of the relative effects of adjustments for fiber size (from PCM to fibers longer than 10 μm and thinner than 0.4 μm) and fiber type toward the goal of rationalizing the K_L and K_M values obtained from different environments, the effect of the two adjustments are considered sequentially—first the effect of adjusting for fiber size is considered and next the added effect of adjusting for fiber type is evaluated.

To compare the effects of adjusting K_L and K_M values for fiber size, the K_{L^*} and K_{M^*} values, which are adjusted to the optimal exposure index (using Equation 7-9) are plotted (along with their associated uncertainty intervals) in Figure 7-3, and 7-4. These figures are in a format identical to that of Figures 7-1 and 7-2 of the untransformed values. The "key" provided for Figure 7-1 is also directly transferable to Figures 7-2, 7-3, and 7-4.

Note that one of the points plotted in Figures 7-1 and 7-2 was omitted from Figures 7-3 and 7-4 (for the Enterline study [1986] of retired factory workers: study MX13) because it was felt that none of the available size distributions were suitably applicable for this study site, so no conversions were possible. Also, the confidence intervals are larger in Figures 7-3 and 7-4 because, as previously indicated, we have attempted throughout our analysis of the epidemiology data to account for major sources of uncertainty. Thus, the confidence intervals depicted in Figure 7-3 and 7-4 are modified from those depicted in Figures 7-1 and 7-2 to account for the uncertainty of making the adjustment for fiber size using paired data from published size distributions. The intervals were adjusted by multiplying the upper bound and dividing the lower bound by a factor thought to represent the relative contribution to uncertainty contributed by the need to match data from separate studies to perform the conversions. The factors employed (along with the rationale for selecting the value of each factor) are provided in Table 7-15.

The visual impressions from a comparison between Figures 7-1 and 7-3 for lung cancer and between Figures 7-2 and 7-4 for mesothelioma are that the changes resulting from adjusting for fiber size are subtle. This visual impression is reinforced by the relative similarity of the fits (based on comparison of σ and log-likelihoods) reported in Table 7-17 for PCME and the optimal exposure index, particularly for lung cancer.

Figures 7-5 and 7-6 show the effects of adjusting exposure-response coefficients for both fiber size and type. To develop Figure 7-5 for lung cancer, a size-adjusted K_L, as plotted in Figure 7-3, was further adjusted to correspond to pure amphibole by dividing it by the factor $[f_{amph} + rpc * (1 - f_{amph})]$, where f_{amp} is the proportion of amphibole fibers estimated for a given environment (as listed in Table 7-16) and rpc=0.267, the optimal value from Table 7-17. The corresponding adjusted factors corresponding to pure chrysotile can be calculated simply by multiplying the amphibole value by rpc=0.267. Since the study-specific values for pure amphibole all differ from the corresponding value for pure chrysotile by a multiplicative constant, values for both types of asbestos are plotted simultaneously in Figure 7-5 by using a different scale for amphibole and chrysotile. The same method was used to develop Figure 7-6 for mesothelioma exposure-response coefficients, from the size-adjusted K_M values plotted in Figure 7-4, the only difference being that the mesothelioma rpc=0.0013 (Table 7-17) was used for this latter conversion. Comparing Figure 7-5 to 7-1 suggests that the adjustments for size and type resulted in as somewhat better reconciliation of the dose-response coefficients for lung cancer, although the improvement is still somewhat subtle. However, a comparison of Figures 7-6 to 7-2 indicates a much more dramatic improvement in the case of mesothelioma. Comparisons of Figures 7-2, 7-4, and 7-6 indicate this is primarily due to the adjustment for fiber type, although the subsequent adjustment for fiber size provides further, noticeable improvement.

Figure 7-3:
Plot of Estimated (Adjusted) K_L- Values and Associated Uncertainty Intervals by Study Environment

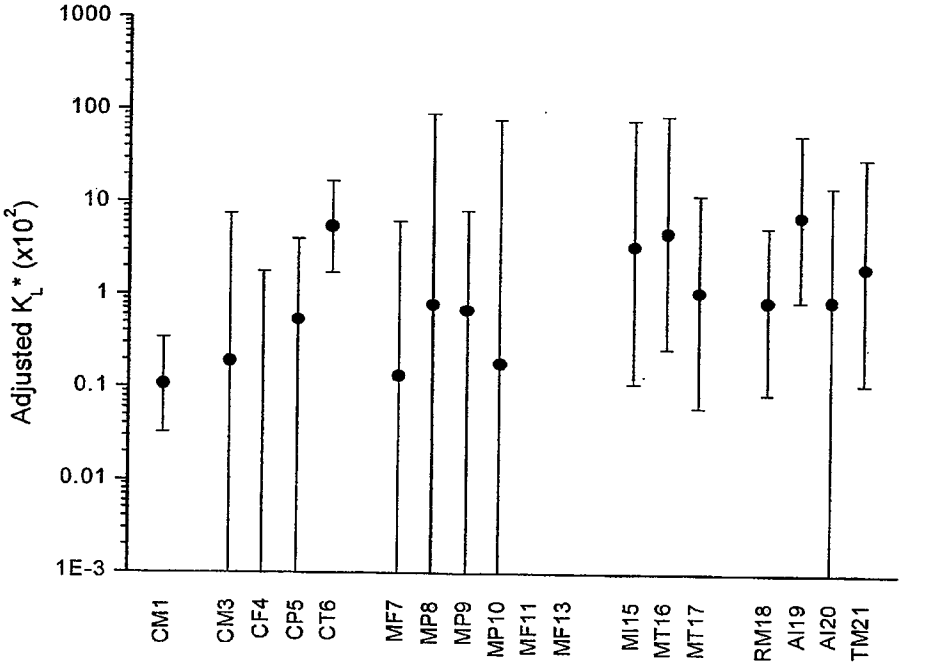
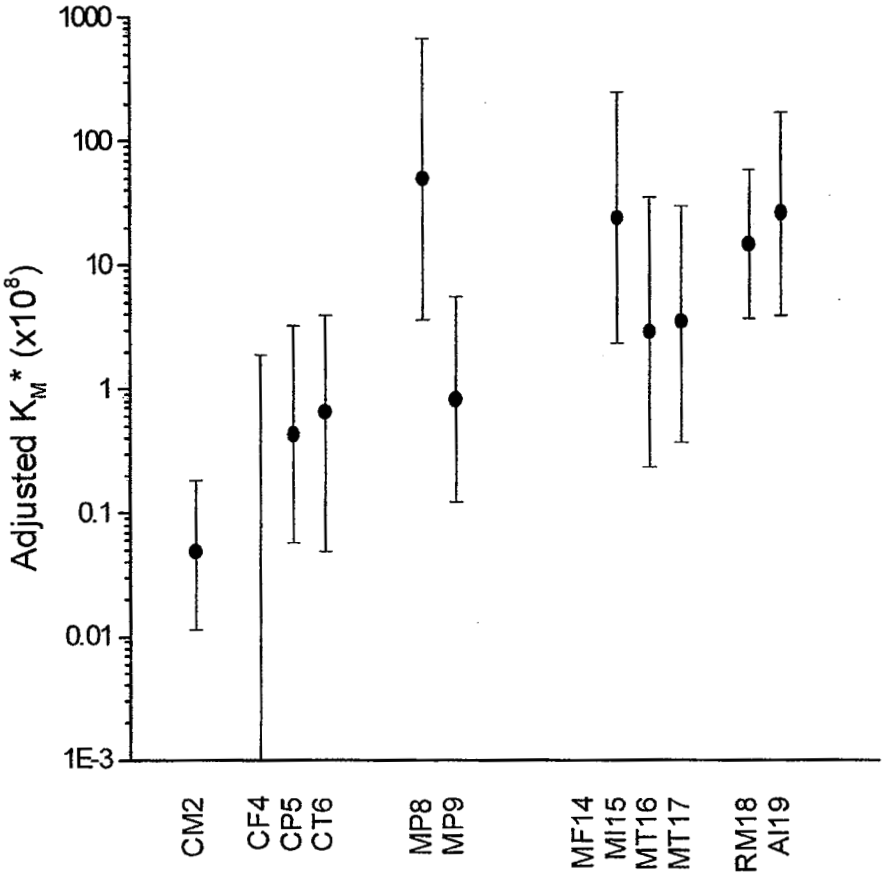


Figure 7-4:
Plot of Estimated (Adjusted) K_M Values and Associated Uncertainty Intervals by Study Environment



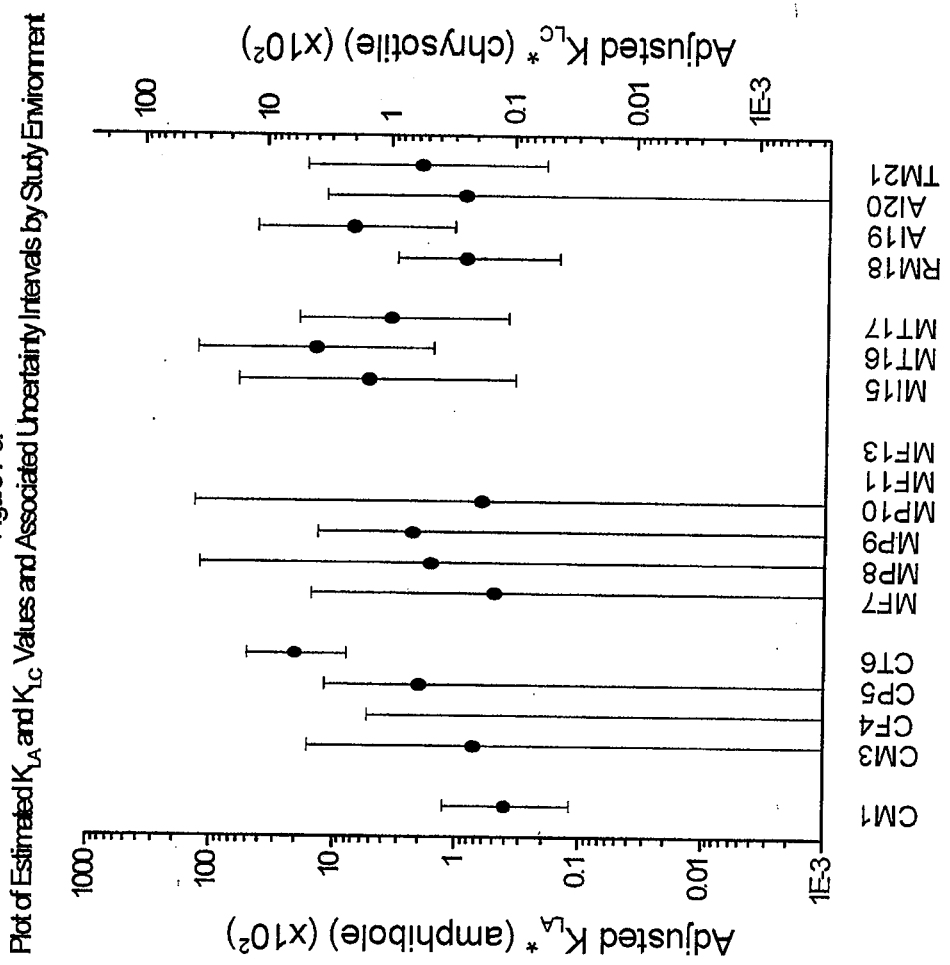
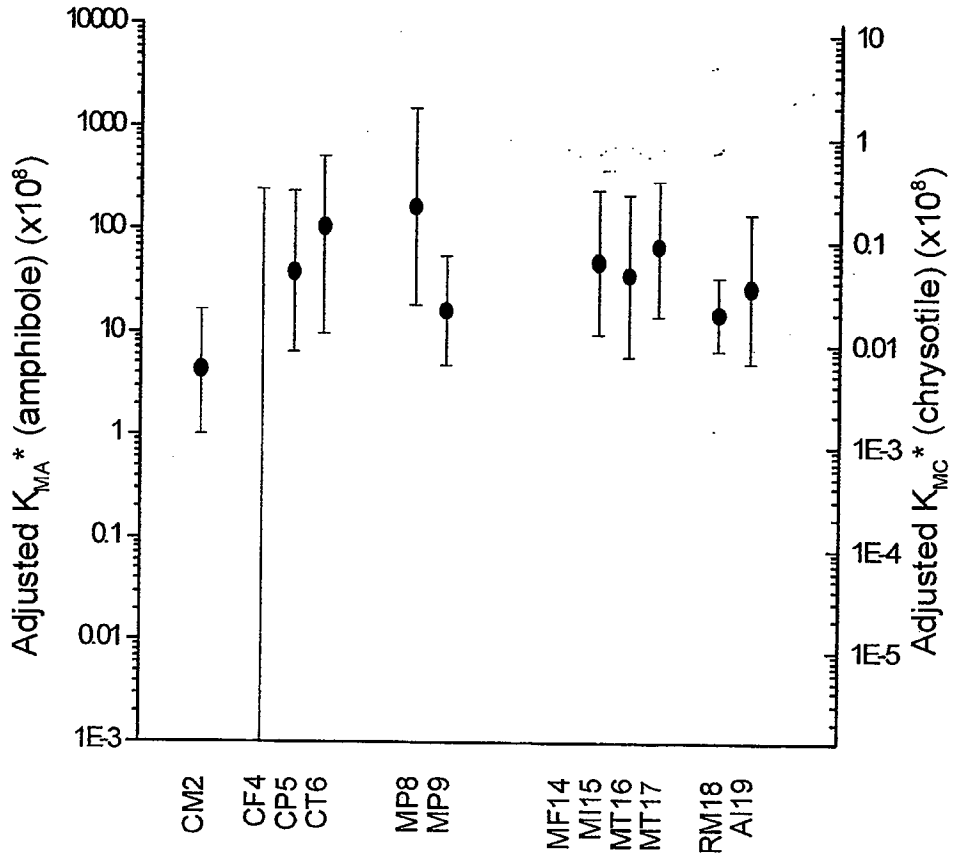


Figure 7-5:
Plot of Estimated K_A and K_{LC} Values and Associated Uncertainty Intervals by Study Environment

Figure 7-6:
Plot of Estimated K_{MA} and K_{MC} Values and Associated Uncertainty Intervals by Study Environment



In addition to the graphical comparisons, it is also instructive to consider numerical comparisons. Table 7-19 reproduces values for all of the original (study-specific) K_L and K_M (from Tables 7-6 and 7-9, respectively) along with all the corresponding values for the adjusted K_{L^*} and K_{M^*}. Study-specific estimates for the all the corresponding K_{LA}, K_{LC}, K_{MA}, and K_{MC} are also presented.

Table 7-20 presents the magnitude of the spread in the range of original and adjusted K_L and K_M values estimated as the quotient of the maximum and minimum values of each range. Note that, of necessity, such an analysis requires that the zero values obtained for the Connecticut friction products plant (CF4) be omitted. Note further that the data sets evaluated in Table 7-20 for the original and adjusted values are identical (i.e., the one study for which no suitable fiber size distribution could be found was excluded).

In Table 7-20, for mesothelioma, the spread in unadjusted values among "pure" fiber types (i.e., chrysotile only or amphibole only) are both substantially smaller than those for mixed data sets (containing both fiber types). This provides further evidence of differences in the potencies of each fiber type toward mesothelioma. It is also apparent that adjusting for fiber size decreases the range within pure fiber types. Moreover, by simultaneously adjusting for both fiber size and type (as illustrated by the column labeled, "K_{mx}"), the range of variability across the entire data set of 10 mesothelioma studies is reduced from almost 1,100 to a factor of 30, which is a clear and substantial improvement.

For lung cancer, the results presented in Table 7-20 are a bit more complicated. While there is a substantial reduction in the spread of unadjusted values among "pure" amphibole environments when mixed environments are excluded, the spread among "pure" chrysotile environments is no different than that observed for the entire data set. This is because, as previously described (Section 7.2.2) the difference between the K_L values observed among chrysotile miners in Quebec and chrysotile textile workers in South Carolina represent the extremes of the entire range of reported K_L values. Adjusting these exposure-response coefficients for size provides some improvement in agreement across these two environments. This reinforces the finding from Appendix D that, if size adjustments incorporating cutoffs for longer fibers could be incorporated into a new exposure index for asbestos, the apparent discrepancy between the exposure-response observed among Quebec miners and South Carolina textile workers (and, thus, among K_L values as a whole) is likely to be further reconciled. The impressions from the figures discussed above and from Table 7-20 confirm the conclusions concerning the quantitative improvement in agreement across exposure-response coefficients highlighted in Sections 7.4.3.1 and 7.4.3.2 and reinforce the conclusion that, especially with regard to mesothelioma, adjusting exposure-response coefficients for fiber size and type leads to substantially improved agreement across studies.

Table 7-19. Study Specific K_l, K_m, K_{l*}, K_{m*}, K_{la}, K_{ma}, K_{lc}, and K_{mc} Values

Environment	Study Code	K_L Reference	K_M Reference	K_L (x100)	K_M ($x10^8$)	K_L' (x100)	K_M' ($x10^8$)	Amphiboles K_{LA} (x100)	Amphiboles K_{MA} (x100)	Chrysotile K_{LC} ($x10^8$)	Chrysotile K_{MC} ($x10^8$)
Quebec mines and mills	CM1	Liddell et al. 1997		0.029		0.108		0.399		0.106	
Quebec mines	CM2		Liddell et al. 1997 (raw data)		0.0165		0.062		5.51		0.00716
Italian mine and mill	CM3	Piolatto et al. 1990		0.051		0.131		0.716		0.190	
Connecticut plant	CF4	McDonald et al. 1984	McDonald et al. 1984	0	0	0	0				
New Orleans plants	CP5	Hughes et al. 1987	Hughes et al. 1987	0.25	0.2	0.864	0.432	1.979	38.3	0.526	0.0498
South Carolina plant	CT6	Dement et al. 1994 (raw data)	Dement 2001 (person. comm.)	2.1	0.25	6.38	0.660	20.7	106	5.50	0.137
Wittenoom, Australia	RM18	DeKlerk, unpublished data	DeKlerk, unpublished data	0.47	7.9	0.87	14.43	0.9	15.08	0.24	0.02
Patterson, NJ factory	AI19	Seidman et al. 1986	Seidman et al. 1986	1.1	3.9	17.36074	26.04111	7.526804	26.9044	2.00213	0.034976
Tyler, Texas factory	AI20	Levin et al. 1998		0.13		0.868037		0.889531		0.236615	
Libby, Montana	TM21	Amandus and Wheeler 1987		0.45		2.44		1.868577		0.497041	
British factory	MF7	Berry and Newhouse 1983		0.058		0.134276		0.498301		0.132548	
Ontario factory	MP8	Finkelstein 1984	Finkelstein 1984	0.29	18	3.246555	48.69833	1.63756	164.2291	0.435591	0.213498

Table 7-19. Study Specific K_l, K_m, K_{l^*}, K_{m^*}, K_{la}, K_{ma}, K_{lc}, and K_{mc} Values *(continued)*

								Amphiboles		Chrysotile	
Environment	Study Code	KL Reference	KM Reference	KL (x100)	KM ($x10^8$)	KL' (x100)	KM' ($x10^8$)	K_{LA} (x100)	K_{MA} (x100)	K_{LC} ($x10^8$)	K_{MC} ($x10^8$)
New Orleans plants	MP9	Hughes et al. 1987	Hughes et al. 1987	0.25	0.3	1.082185	0.811639	2.267472	16.07566	0.603147	0.020898
Swedish plant	MP10	Albin et al. 1990		0.067		0.189382		0.638655		0.169882	
Belgium factory	MP11	Laquet et al. 1980		0.0068							
U.S. retirees	MX13	Enterline et al. 1986		0.11							
Asbestos, Quebec	MX14		Liddell et al. 1997 (raw data loc 2)		0.092						
U.S. insulation workers	MI15	Selikoff and Seidman 1991	Selikoff and Seidman 1991	0.18	1.3	7.411067	24.08597	5.331754	48.68671	1.418246	0.063293
Pennsylvania plant	MT16	McDonald et al. 1983b	McDonald et al. 1983b	1.8	1.1	4.781501	2.922028	14.72572	35.9891	3.917041	0.046786
Rochedale, England plant	MT17	Peto et al. 1985	Peto et al. 1985	0.41	1.31	2.39075	3.47987	3.598193	67.9231	0.957119	0.0883

Table 7-20. Comparison of Spread in Range of Original and Adjusted K_l and K_m Values for Specific Fiber Types

Fiber Type	Ranges of Values							
	Number in K_L, K_{L*},K_{LX} Sets	K_L	K_{L*}	K_{LX}	Number in K_M, K_{M*},K_{MX} Sets	K_M	K_{M*}	K_{MX}
All fiber types combined	15	72	67	52	10	1,089	795	30
Chrysotile only (excluding mixed)	4	72	51	52	3	15	11	19
Chrysotile only (also excluiding textiles)	3	8.6	5.0	5.0	2	12	7.0	7.0
Chrysotile and mixed settings	11	72	51	52	8	1,089	794	30
Textiles only	3	5.1	5.1	5.7	3	5.2	5.2	2.9
Amphibole and mixed settings	11	31	55	30	7	60	60	11
Amphiboles only (excluding mixed)	4	8.5	8.5	8.5	2	2.0	1.7	1.7

7.6 GENERAL CONCLUSIONS FROM QUANTITATIVE ANALYSIS OF HUMAN EPIDEMIOLOGY STUDIES

The following conclusions result from our evaluation of the available epidemiology studies.

(1) To study the characteristics of asbestos that relate to risk, it is necessary to combine results (i.e., in a meta analysis) from studies of environments having asbestos dusts of differing characteristics. More robust conclusions regarding risk can be drawn from an analysis of the set of epidemiology studies taken as a whole than results derived from individual studies.

(2) By adjusting for fiber size and fiber type, the existing database of studies can be reconciled adequately to reasonably support risk assessment.

(3) The U.S. EPA models for lung cancer and mesothelioma both appear to track the time-dependence of disease at long times following cessation of exposure, however, the relationship between exposure concentration and response may not be adequately described by the current models for either disease. There is some evidence that these relationships are supra-linear.

(4) Whereas the U.S. EPA model for lung cancer assumes a multiplicative relationship between smoking and asbestos, the current evidence suggests that the relationship is less than multiplicative, but possibly more complex than additive. However, even if the smoking-asbestos interaction is not multiplicative as predicted by the U.S. EPA model, exposure-response coefficients estimated from the model are still likely to relate to risk approximately proportionally and, consequently, may be used to determine an exposure index that reconciles asbestos potencies in different environments. However, adjustments to the coefficients may be required in order to use them to estimate absolute lung cancer risk for differing amounts of smoking. This issue needs to be investigated further in the next draft of this document.

(5) The optimal adjustment found for fiber size and type that best reconciles the published literature assigns equal potency to fibers longer than 10 μm and thinner than 0.4 μm and assigns no potency to fibers of other dimensions. Different exposure-response coefficients for chrysotile and amphibole are assigned both for lung cancer and mesothelioma. For lung cancer the best estimate of the coefficient (potency) for chrysotile is 0.27 times that for amphibole, and for mesothelioma the best estimate of the coefficient (potency) for chrysotile is only 0.0013 times that for amphibole.

(6) Without adjustments, the lung cancer exposure-response coefficients (K_L values) estimated from 15 studies vary by a factor of 72 and these values are mutually inconsistent (based on non-overlap of uncertainty intervals). By simultaneously adjusting these values for fiber size and type, the overall variation in K_L values across these studies is reduced to a factor of 50.

(7) Without adjustments, the mesothelioma exposure-response coefficients (K_M values) estimated from 10 studies vary by a factor of 1,089, and these values are likewise mutually inconsistent. By simultaneously adjusting these values for fiber size and type, the overall variation in K_M values across these studies is reduced to a factor of 30.

(8) The exposure index and exposure-response coefficients embodied in the risk assessment approach developed in this report are more consistent with the literature than the current U.S. EPA approach. In particular, the current approach appears highly likely to seriously underestimate risk from amphiboles, while possibly overstating risk from chrysotile. Furthermore, most the remaining uncertainties regarding the new proposed approach also apply to the current approach. Consequently, we recommend that the proposed approach begin to be applied in assessment of asbestos risk on an interim basis, while further work, as recommended below, is being conducted to further refine the approach.

(9) The residual inconsistency in both the lung cancer and mesothelioma potency values is primarily driven by those calculated from Quebec chrysotile miners and from South Carolina chrysotile textile workers. The difference in the lung cancer potency estimated between these studies has long been the subject of much attention. A detailed evaluation of the studies addressing this issue, the results of our analysis of the overall epidemiology literature, and implications from the broader literature, indicate that the most likely cause of the difference between these studies is the relative distribution of fiber sizes in the two environments. It is therefore likely that the variation between these studies can be further

reduced by developing improved characterizations of the dusts that were present in each of these environments (relying on either archived samples, or newly generated samples using technologies similar to those used originally).

Recommendations for Limited, Further Study

The two major objectives identified above for further study are:

(1) to evaluate a broader range of exposure-response models in fitting the observed relationship between asbestos exposure and lung cancer or mesothelioma, respectively. For lung cancer models, this would also include an attempt to better account for the interaction between asbestos exposure and smoking; and

(2) to develop the supporting data needed to define adjustments for exposure-response coefficients that will allow them to be used with an exposure index that more closely captures the criteria that determine biological activity (see Section 6.5). Among other things, this work should focus on obtaining data that would permit more complete reconciliation of the exposure-response coefficients derived for Quebec miners and South Carolina textile workers.

The first of the above objectives requires access to raw data from a small number of selected, additional epidemiology studies. The best candidate studies include: (for chrysotile) the lung cancer data from Quebec (best) or, potentially, from the New Orleans asbestos-cement pipe plant studied by Hughes et al. For amphiboles, the best candidate studies include: the lung cancer and *newest* mesothelioma data from Libby, or, potentially the lung cancer and mesothelioma data from the Paterson, New Jersey insulation manufacturing plant studied by Seidman et al. (1986). The possibility of obtaining some or all of these data sets needs to be further explored.

The second of the above objectives requires more detailed size characterization data for the environments of interest. Although archived air samples do not appear to be available from any of the study locations of interest (except South Carolina), we believe that suitable data can be developed from appropriate bulk samples. Thus, for example, it would be useful to obtain samples of the raw ore from Libby, Wittenoom, and Quebec and the textile, asbestos-cement pipe, and friction-product grade products from Quebec.

Results from our review of the supporting literature suggest that the optimum cutoff for increased potency occurs at a length that is closer to 20 μm than 10 μm, (the latter of which is the cutoff in the exposure index provided in this study). Data do not currently exist to improve on this latter cutoff. However, provided that study-specific size distribution data could be obtained as indicated above, with the appropriate analyses, it will be possible to develop the size distributions necessary to evaluate a range of considerations including:

(1) delineation of size fractions among individual length categories out to lengths as long as 30 or 40 μm;

(2) determination of the relative presence and importance of cleavage fragments (of non-biologically relevant sizes) in mine ores vs. finished fibers; and

(3) the relative fraction of fibrous material vs. non-fibrous particles in the various exposure dusts of interest.

8.0 DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

Although gaps in knowledge remain, a review of the literature addressing the health-related effects of asbestos (and related materials) provides a generally consistent picture of the relationship between asbestos exposure and the induction of disease (lung cancer and mesothelioma). Therefore, the general characteristics of asbestos exposure that drive the induction of cancer can be inferred from the existing studies and can be applied to define appropriate procedures for evaluating asbestos-related risk. Moreover, such procedures provide substantial improvement in the confidence that can be placed in predicting risks in exposure environments of interest compared to risk predictions based on procedures in current use.

Following a general discussions of the findings of this study, specific recommendations for finalizing a protocol for assessing asbestos-related risks using the procedures identified in this document are provided in Section 8.2. Recommendations are described in Section 8.3 for limited, focused, additional studies to:

(1) settle a small number of outstanding issues (concerning whether better models exist than the current U.S. EPA models for tracking the time and concentration dependence of the exposure-response relationships for asbestos-induced lung cancer and mesothelioma);

(2) improve the manner in which smoking is addressed in the modeling of asbestos-induced lung cancer; and

(3) provide the data required to fully optimize the approach recommended in this document (i.e., reconciling the published epidemiology studies by addressing the effects of fiber size and type).

Moreover, these recommendations parallel those of the expert panel convened to peer-review the previous version of this report (Appendix B).

8.1 DISCUSSION AND CONCLUSIONS

8.1.1 Addressing Issues

The issues identified in the introduction (Chapter 2) as part of the focus of this study can now be addressed. These are:

- adequacy of existing models: whether the exposure-response models currently in use by the U.S. EPA for describing the incidence of asbestos-related diseases adequately reflect the time- and exposure-dependence for the development of these diseases;

- relative potency for different mineral types: whether different potencies need to be assigned to the different asbestos mineral types to adequately predict risk for the disease endpoints of interest;

- biodurability: to the extent that different asbestos mineral types are assigned distinct potencies, whether the relative *in vivo* durability of different asbestos mineral types determines their relative potency;

- minerals of concern: whether the set of minerals included in the current definition of asbestos adequately covers the range of minerals that potentially contribute to asbestos-related diseases;

- analytical methods: whether the analytical techniques and methods currently used for determining asbestos concentrations adequately capture the biologically-relevant characteristics of asbestos (particularly with regard to structure sizes), so that they can be used to support risk assessment; and

- extrapolation of risk coefficients: whether reasonable confidence can be placed in the cross-study extrapolation of exposure-response relationships that are required to assess asbestos-related risks in new environments of interest.

The Adequacy of Existing Models. Regarding the first of the above-listed issues, both the U.S. EPA lung cancer model and mesothelioma model appear to adequately reflect the time-development of asbestos-induced lung cancer. For lung cancer, the assumption in the model that risk remains constant with time following the end of exposure was confirmed for cohorts exposed, respectively, to chrysotile, to crocidolite, and to amosite (Section 7.2.1). A similar analysis for mesothelioma suggests that, as that model predicts, risk for mesothelioma continues to increase with the square of time since the end of exposure (Section 7.3.1).

Regarding exposure concentration, we did find some evidence suggesting that, for both lung cancer and mesothelioma, the relationship between exposure concentration and risk may not be linear, but rather supra-linear (Sections 7.2.1.1 and 7.3.1.2). If confirmed, this would contradict the assumed strictly linear relationship in both the current lung cancer and mesothelioma models.

For 15 of the 18 studies that were fit using the lung cancer model (Equation 7-2) in our analysis (Appendix A and Section 7.2.2), the parameter, α, (which indicates differences in background lung cancer incidence between cohorts and controls) was greater than 1.0 and significantly so in six cases. In these cases, if it is assumed instead that the background lung cancer mortality rate applied to the cohort is appropriate, the correct fitting would be with $\alpha=1.0$, in which case the exposure-response would appear supra-linear. Similarly, an analysis conducted using the raw data from Wittenoom (Section 7.3.1.2) in which exposure is categorized by intensity while controlling for both time since the end of exposure and duration of exposure suggests a supra-linear relationship between exposure concentration and mesothelioma as well.

Due to these observations and additional concerns about the relationship between smoking and asbestos exposure toward the induction of lung cancer (Section 7.2.1.3), evaluation of the fit of a broader range of models to the available lung cancer and mesothelioma data is recommended.

Importantly, because any such evaluation would be greatly enhanced by broadening the number of data sets utilized, it is further recommended that all means be explored for acquiring raw data sets for cohorts from additional epidemiology studies.

At the same time, although there are suggestions from our analysis that models other than the current models might better describe the relationship between exposure and risk for both mesothelioma and lung cancer any limitation associated with use of the current models for lung cancer and mesothelioma would be common to the procedures recommended in this report and the existing U.S. EPA approach for assessing asbestos-related risks. Therefore, given the degree of improvement demonstrated for the proposed approach over the current U.S. EPA approach, there appears to be little reason not to adopt the proposed approach as an interim measure, while further research is conducted to address the remaining outstanding issues highlighted by the expert panel (Appendix B) and highlighted in this report.

Relative Potency for Different Mineral Types. As indicated in Sections 7.4.3.2 and 7.5.2, our analysis indicates a substantial difference in the relative potency of amphiboles and chrysotile toward the induction of mesothelioma, with amphiboles estimated as almost 1,000 times more potent than chrysotile (fiber-for-fiber). Moreover, this difference was shown to be highly statistically significant. When fiber size and type are simultaneous addressed, variation across the 10 published epidemiology studies included in our analysis drops from a factor of more than 1,000 to a factor of 30 (Table 7-19). This, coupled with the growing evidence in the literature supporting this difference in potency among fiber types, provides strong support for defining distinct risk coefficients for chrysotile and the amphiboles to assess the risk of mesothelioma.

The situation with lung cancer is less clear. Although our analysis suggests that the best estimate is that (fiber-for-fiber) amphiboles are about 4 times more potent than chrysotile toward the induction of lung cancer, this difference was not found to be statistically significant (Sections 7.4.3.1 and 7.5.2). This issue also remains unresolved in the wider literature. It is also possible that the confounding effects of smoking, coupled with the lack of adequate data for properly assessing the effects of smoking may be limiting our ability to address this question. Thus, this is one of the issues that would likely benefit from additional research.

At the same time, when a small difference in potencies is incorporated into our meta analysis of the epidemiology studies we evaluated, variation across the data set is reduced by about 30% (Table 7-20). This suggests that incorporating a small difference in lung cancer risk coefficients for chrysotile and the amphiboles is reasonable.

Biodurability. Because the *in vitro* dissolution rate for chrysotile in biological fluids is substantially greater than for crocidolite and, likely, other amphiboles (Section 6.2.4), effects potentially attributable to differences in the relative biodurability of these asbestos types are addressed in several sections of this document. It is possible that such differential biodurability at least partially explains the clear difference in potency between chrysotile and the amphiboles toward mesothelioma (along with the possible, albeit smaller, difference toward lung cancer). However, that no difference was observed in the time-development of either lung cancer or mesothelioma following exposure to chrysotile or amphibole asbestos (respectively) suggests that any relationship that exists between potency and biodurability must be more subtle and complicated than the obvious effect on internal dose. At the same time, there is ample literature

evidence that some kind of relationship in fact exists (Section 6.2.4). While more research into this relationship may prove interesting (and may be useful for assessing effects of less durable fibers), it is unlikely to have a direct impact on procedures for assessing asbestos-related risk.

Minerals of Concern. Regarding the range of fibrous minerals that potentially contribute to lung cancer and mesothelioma, available evidence (Sections 6.2 and 6.4) suggests that:

- several minerals and the most biodurable among synthetic fibers (such as erionite or refractory ceramic fibers) in addition to those included strictly within the definition for asbestos have been shown capable of inducing lung cancer and/or mesothelioma (as long as the corresponding fibers fall within the appropriate size range);

- fibrous minerals that differ radically in chemical composition or crystal structure (such as erionite, chrysotile, and the amphibole asbestos types) appear to exhibit substantially different potencies (even after adjusting for size); and

- fibrous minerals that exhibit closely related chemical compositions and crystal structures (such as the family of amphibole asbestos types) appear to exhibit relatively similar potencies (once effects are adjusted for size). To illustrate this point for mesothelioma, consider that the range of variation in estimated K_M's over 10 studies (which include studies of exposures to tremolite, amosite, and crocidolite in addition to chrysotile) is reduced to a factor of 30 (from almost 1,100), once the effects of size and differences between the amphiboles and chrysotile are accounted for (Table 7-20). Moreover, among the 7 of these studies reflecting exposure exclusively to amphiboles (which still includes exposures to tremolite[1], crocidolite, and amosite), the range of variation is reduced to a factor of 11 (Table 7-20). Regarding lung cancer, the four studies of "pure" amphibole environments (which includes exposures to tremolite, crocidolite, and amosite) vary by only a factor of 8.5 (Table 7-20) and this range is bounded by studies of the same mineral: amosite, which certainly suggests that mineralogical differences do not drive the observed variation (Section 7.2.2).

Given the above-described observations, it is clear that fibrous minerals beyond those included in the definition for asbestos can contribute to lung cancer and mesothelioma. It is also likely that potencies for minerals that exhibit similar chemistry and crystal structure (and which therefore likely exhibit similar physical-chemical properties) also exhibit corresponding potency (for similarly sized fibers). However, the carcinogenicity of fibers exhibiting radically different chemical compositions and crystal structures than those already identified as carcinogenic should be evaluated on a case-by-case basis.

Two additional considerations may be useful for focusing such evaluations. First, the size distribution for fibers composed of the mineral of concern should be shown to include substantial

[1]Formally, the exposures at Libby are to the amphibole mineral richterite. However, this mineral is closely related to tremolite and has sometimes been called "sodium tremolite" because it contains a greater fraction of sodium than the composition range that is commonly termed tremolite.

numbers within the range of structures that potentially contribute to biological activity (e.g., that fall within the size range defined by the improved index recommended in this study, i.e., structures longer than 10 μm and thinner than 0.4 μm, see Section 7.5). Second, such fibers should also be shown to be relatively biodurable (i.e., that they exhibit dissolution rates less than approximately 100 ng/cm^2-hour, Lippmann 1999).

Analytical Methods. Given the need to detect the thinnest fibers and the need for reliable measurements in outdoor settings, the only analytical technique that appears to be capable of providing quantitative data useful for supporting risk assessment is TEM (Sections 4.3 and 7.6). Further, given the specific size range of structures that need to be evaluated and the specific manner in which they need to be counted (to assure both cross-study comparability and compatibility with the recommended dose-response coefficients), analyses should be performed using the specific analytical methods recommended in this document. These are ISO 10312 (modified to focus on interim index structures) for air and the Modified Elutriator method (Berman and Kolk 2000) for soils or bulk materials. However, on a study-specific basis, other methods may be shown to provide comparable results so that they can also be used as part of a properly integrated investigation.

8.1.2 Comparison with Other, Recent Risk Reviews

Although several other reviews have also recently been published that nominally address risk-related issues for asbestos (including questions concerning the identification of an appropriate exposure index and the relative potency of varying fiber types), these studies are either qualitative or involve analysis of data in a manner that does not allow formal evaluation of the nature of specific exposure-response relationships for the various diseases. Therefore, they are not well suited to support development of a protocol for conducting formal assessment of asbestos-related risks. Nevertheless, the general conclusions from these reviews are not inconsistent with our findings.

Hodgson and Darnton (2000). Hodgson and Darnton (2000) conducted a comprehensive quantitative review of potency of asbestos for causing lung cancer and mesothelioma in relation to fiber type. They concluded that amosite and crocidolite were, respectively, on the order of 100 and 500 times more potent for causing mesothelioma than chrysotile. They regarded the evidence for lung cancer to be less clear cut, but concluded nevertheless that amphiboles (amosite and crocidolite) were between 10 and 50 times more potent for causing lung cancer than chrysotile. In reaching this latter conclusion they discounted the high estimate of chrysotile potency obtained from the South Carolina cohort. Hodgson and Darnton concluded that inter-study comparisons for amphibole fibers suggested non-linear exposure-response relationships for lung cancer and mesothelioma, although a linear relationship was possible for pleural mesothelioma and lung tumors, but not for peritoneal mesothelioma.

The Hodgson and Darnton study was based on 17 cohorts, 14 of which were among the 20 included in the present evaluation. This study had different goals from the present evaluation and used different methods of analysis. Hodgson and Darnton did not use the exposure-response information within a study. Instead, lung cancer potency was expressed as a cohort-wide excess mortality divided by the cohort mean exposure. Likewise, mesothelioma potency was expressed as the number of mesothelioma deaths divided by the expected total number of deaths,

normalized to an age of first exposure of 30, and by the mean exposure for the cohort. These measures have the advantage of being generally calculatable from the summarized data available from a study. However, since they are not model-based, it is not clear how they could be used to assess lifetime risk from a specified exposure pattern, which is an important goal of the current project. Use of average cohort exposure could cause biases in the estimates, if, e.g., a large number of subjects were minimally exposed. Also, the recognized differences between studies in factors, in addition to level of exposure, that may affect risk will also affect the reliability of conclusions concerning the dose response shape based on comparisons of results across studies.

Lippmann (1994, 1999). In the most recent of these reviews, Lippmann (1999) reinforces our general findings that it is longer fibers (those longer than a minimum of approximately 5 μm) that contribute to lung cancer and mesothelioma. He further indicates that, based primarily on the limits observed for fibers that can be phagocytized, fibers that contribute most to lung cancer are likely longer than a minimum of 10 μm. In his review, based on a series of comparisons of mean and median dimensions reported for the relevant exposures across a broad range of studies, Lippmann draws several fairly specific conclusions on the ranges of fiber sizes that may contribute to various diseases (i.e., that the minimum length fibers that contribute to asbestosis, lung cancer, and mesothelioma are 2, 5, and 10 μm, respectively). He also suggests that fibers that contribute to mesothelioma may need to be thinner than 0.1 μm while those that contribute to lung cancer may need to be thicker than 0.15 μm. While it is not clear that drawing such specific conclusions can be firmly supported by the kinds of qualitative comparisons across reported mean and median dimensions for exposures in various studies that are described in this paper, the author indicates that further, more formal study of the dose-response relationships that he posits is warranted. It is noted that many of the studies reviewed by Lippmann (1999) are also incorporated in our analysis.

In the earlier review, Lippmann (1994) plots lung tumor incidence as a function of inhaled animal dose for data from a series of broadly varying studies based, respectively, on fibers longer than 5, 10, and 20 μm (no widths considered) and suggests that the quality of the fits are comparable. The author further suggests, based on this evaluation, that PCM seems to provide a reasonable index of exposure. However, no formal goodness-of-fit tests were performed in this analysis and, based on visual inspection, none of the plots would likely show an adequate fit. Moreover, the plot of the tumor response vs. dose as a function of fibers longer than 5 μm appears to be substantially worse than the other two plots; if one removes the single highest point in this plot, it appears that any correlation will largely disappear.

Stayner et al. 1996. In the context of evaluating the "amphibole hypothesis", Stayner et al. (1996) computed the excess relative risk of lung cancer per fiber/ml/year from 10 studies categorized by the fiber types to which the cohort was exposed. Each of these studies was also included in the present evaluation. Both the lowest and highest excess relative risks came from cohorts exposed exclusively to chrysotile. Based on their evaluation, they concluded that the epidemiologic evidence did not support the hypothesis that chrysotile asbestos is less potent than amphibole for inducing lung cancer. However, based on a review of the percentage of deaths in various cohorts from mesothelioma, they concluded that amphiboles were likely to be more potent than chrysotile in the induction of mesothelioma. They also noted that comparison of the potency of different forms of asbestos are severely limited by uncontrolled differences in fiber sizes. None of these conclusions are inconsistent with our general findings.

8.2 RECOMMENDATIONS FOR ASSESSING ASBESTOS-RELATED RISKS

The optimum values for the risk coefficients for lung cancer and mesothelioma (the adjusted K_L and K_M values) derived in our analysis are provided in Table 7-18. Although these values are optimized (within the constraints of the current analysis) and use of these values reduces the apparent variation across published studies substantially (Section 7.5.2), the need to manage and minimize risk when developing a general approach for assessing risk, is also recognized. Thus, to reduce the chance of under-estimating risks, a conservative set of potency estimates were developed (Table 8-1) by adjusting upward the best-estimate potency coefficients listed in Table 7-18 to provide additional health protectiveness. The manner in which this was accomplished is described in the following paragraphs.

Table 8-1. Conservative Risk Coefficients for Pure Fiber Types

Fiber Type	$K_{L^*} \times 100$	$K_{M^*} \times 10^8$
Chrysotile	5.5	0.15
Amphiboles	20	100

Reviewing the K_{Lc} and K_{La} dose response coefficients values listed in Table 7-19, it is apparent that the maximum values for lung cancer derive from the Dement et al. (1994) study of the South Carolina textile plant. As indicated in Appendix A, the South Carolina study is a high quality study. Moreover, we were able to obtain the raw data from this study and have analyzed these data in detail. We found, among other things, a well-behaved (i.e., monotonic) exposure-response trend in this study for lung cancer. Therefore, because this study is of high quality and provides the largest values of K_{Lc} and K_{La}, the values from this study were selected for our conservative estimates of the corresponding potency coefficients.

Reviewing the K_{Ma} and K_{Mc} values listed in Table 7-19, it is apparent that the maximum values derive from the Finkelstein study (1984) of the Ontario asbestos-cement factory. As indicated in Appendix A, the data from this study appear problematic. Among other things, the exposure-response relationships observed in this study are not well-behaved (i.e., not monotonic). Moreover, the value for α estimated for this study is the highest of any study we evaluated. Possible reasons for such a large α include large discrepancies between the background incidence of lung cancer between cohort and controls in this study and/or serious errors in exposure estimates. Given the potential problems associated with this study, (which suggests that the potency coefficients estimated from this study may be less reliable than for many of the other available studies), we decided to bypass this study and select the next highest values in Table 7-19 for K_{Ma} and K_{Mc} as the conservative estimates to be recommended in this study. Interestingly, these also turn out to be from the South Carolina textile study. Note that the difference in the estimates from these two studies vary by less than a factor of two in any case.

Based on the above evaluation, conservative estimates for the various potency coefficients recommended in this report are presented in Table 8-1.

Importantly, a measure of the degree of reconciliation among the results of the published epidemiology studies that has been accomplished by the analysis presented in this report is indicated by the ratios of the values presented in Tables 7-18 and 8-1, respectively. The ratios between the corresponding coefficients in Tables 7-18 and 8-1 are no more than 10 for the lung cancer potency coefficients and no more than 4 for the mesothelioma potency coefficients. Moreover, the bounding study for the values presented in Table 8-1 is once again the South Carolina textile study, which further reinforces earlier discussions identifying the particular need to reconcile this study with the other chrysotile studies (particularly the Quebec mining study).

To assess risk, depending on the specific application, either the best-estimate risk coefficients presented in Table 7-18 or the conservative estimates presented in Table 8-1 can be incorporated into procedures described below for assessing asbestos-related risks.

Tables 8-2 and 8-3 present estimates of the additional risk of death from lung cancer, from mesothelioma, and from the two diseases combined that are attributable to lifetime, continuous exposure at an asbestos concentration of 0.0001 f/cm^3.(for fibrous structures longer than 10 μm and thinner than 0.4 μm) as determined using TEM methods recommended herein. Table 8-2 was developed using the best-estimate values for risk coefficients defined in Table 7-18, and Table 8-3 was developed using the conservative estimates defined in Table 8-1. Separate risk estimates are provided for males and females and for smokers and non-smokers. The method used to construct these tables is described in detail in Appendix E.

Separate estimates are presented for smokers and nonsmokers because the lifetime asbestos-induced risk of both lung cancer and mesothelioma differ between smokers and non-smokers. The asbestos-induced risk of lung cancer is higher among smokers because the lung cancer model (Equation 7-2) assumes that the increased mortality rate from lung cancer risk due to asbestos exposure is proportional to background lung cancer mortality, which is higher among smokers. Note that, while this is consistent with a multiplicative effect between smoking and asbestos exposure that has been reported by several researchers (see, for example, Hammond et al. 1979), some of the latest studies of the interaction between smoking and asbestos exposure suggest a more complicated relationship (Section 7.2.1.3). This issue needs to be addressed more fully in future analyses of these data. However, we believe the effects of such considerations on the overall accuracy of asbestos-related risk estimates is likely to be small relative to other sources of error.

Table 8-2. Estimated Additional Deaths from Lung Cancer or Mesothelioma per 100,000 Persons from Constant Lifetime Exposure to 0.0001 TEM f/cc Longer than 10 um and Thinner than 0.4 um – Based on Optimum Risk Coefficients (Table 7-18)

Chrysotile				
	NonSmokers		**Smokers**	
	Males	**Females**	**Males**	**Females**
Lung Cancer	0.185	0.207	1.6	1.5
Mesothelioma	0.0836	0.096	0.0482	0.0702
Combined	0.269	0.303	1.65	1.57
Amphibole				
Lung Cancer	0.2	0.286	2.22	2.47
Mesothelioma	62.7	72.3	36.1	52.7
Combined	62.9	72.5	38.3	55.1

Table 8-3. Estimated Additional Deaths from Lung Cancer or Mesothelioma per 100,000 persons from Constant Lifetime Exposure to 0.0001 TEM f/cc Longer than 10 um and Thinner than 0.4 um - Based on Conservative Risk Coefficients (Table 8-1)

Chrysotile				
	Non-Smokers		**Smokers**	
	Males	**Females**	**Males**	**Females**
Lung Cancer	1.7	1.9	14.7	13.8
Mesothelioma	0.314	0.361	0.181	0.263
Combined	2.02	2.26	14.9	14
Amphibole				
Lung Cancer	3.77	4.41	34.1	33.2
Mesothelioma	209	241	120	175
Combined	213	245	154	209

If there is a desire to generate population averaged risks, this can also be accomplished using the data in Tables 8-2 or 8-3. For such a case, simply choose the appropriate row (for lung cancer, mesothelioma, or combined risk) from either Table 8-2 or 8-3 and substitute the four values given in the row into the following equation to derive a single, population averaged risk:

$$R_{avg} = 0.5*[0.214*(MS + FS) + 0.786*(MNS + FNS) \quad \text{(Eq. 8-1)}$$

Where:

R_{avg}	is the population averaged risk for the chosen disease endpoint;
MS	is the corresponding risk for male smokers;
FS	is the corresponding risk for female smokers;
MNS	is the corresponding risk for male non-smokers; and
FNS	is the corresponding risk for female non-smokers.

Note that Equation 8-1 is derived based on the assumption that 21.4% of the general population smokes (see Appendix E).

The asbestos-induced risk of mesothelioma is smaller among smokers because the mesothelioma model (Equation 7-6) assumes that risk from constant exposure increases rapidly with age, with the result that the predicted mortality rate is highest among the elderly. Thus, since smokers have a shorter life span than non-smokers, their risk of dying from mesothelioma is also predicted to be smaller.

Risks from lifetime exposures to asbestos levels other than 0.0001 may be estimated from the appropriate entry in Tables 8-2 or 8-3 by multiplying the value in the selected cell from the table by the airborne asbestos concentration of interest and dividing by 0.0001 (i.e., by assuming that the additional risk is proportional to the asbestos exposure level). Airborne asbestos concentrations to be used in this manner *must* be estimates of lifetime average exposure and *must* be expressed as structures longer than 10 μm and thinner than 0.4 μm derived as described below.

Importantly, the risks provided in Tables 8-2 and 8-3 relate to exposure estimates expressed in terms of the interim exposure index (i.e., estimates including *only* asbestos structures longer than 10 μm and thinner than 0.4 μm). Only exposures expressed in terms of the same exposure index can be used to adjust the risk estimates to other levels of exposure (in the manner described above). Use of exposures expressed in terms of any other index of exposure (such as the PCME index in current use) will result in invalid estimates of risk.

The procedure described above for estimating risks using Tables 8-2 or 8-3 should provide good approximations as long as the projected risk is no greater than 1,000 per 100,000. Risks greater than 1,000 per 100,000 (i.e., 1 in 100) that are derived from the tables are likely to be over-estimated. However, for risks associated with short-duration exposures or exposures that differ radically over time, it may be better to use a lifetable analysis or a modified version of Tables 8-2 or 8-3 that reflect the differences in exposure duration and frequency. This is to avoid substantially under- or over-estimating risk (depending on how the table might otherwise be applied).

Tables 8-2 and 8-3 were derived using the approach described in Appendix E by incorporating the age-, sex-, and smoking-specific death rates reported for the general U.S. population and assuming that exposure is constant and continuous at the level indicated in the table. The underlying models are provided in Chapter 7 for cases in which exposure is not constant throughout life and for which sufficient data exist to characterize the time-dependence of such exposure. If available, there may also be cases in which it is advantageous to employ mortality data from a control population that better matches the exposed population of interest than the U.S. population as a whole.

For the interim, it is recommended that asbestos-related risks from constant low-level exposures be estimated using Tables 8-2 and 8-3. Although it is possible also to use the tables to estimate risk from short-term exposures by applying the corresponding long-term average exposure *(derived from appropriate measurements, as described below)*, this method can result in significant errors in some cases. It is anticipated that a flexible and user-friendly software package for evaluating risk will eventually be developed to supplement this document. Such a package will be capable of accurately implementing the calculation method presented in Appendix E to calculate risks from general exposure patterns, rather than from constant exposures only.

Requirements for Asbestos Measurements. One additional advantage of the approach for evaluating asbestos-related risks recommended in this document (in comparison to the current approach) is that the procedure for assessing risks is tied unambiguously to a specific index for measuring and expressing exposure (i.e., the index of all fibrous structures longer than 10 μm and thinner than 0.4 μm, as defined in Section 7.5) and this, in turn, is tied unambiguously to requirements for analyzing asbestos samples.

Estimates of airborne asbestos concentrations that are required to support risk assessment can be derived either by extrapolation from airborne measurements or by modeling release and dispersion of asbestos from sources (soils or other bulk materials). In either case, exposure estimates must be representative of actual (time-dependent) exposure and must provide measurements that include only fibrous structures satisfying the dimensional criteria listed in the last paragraph. Additional considerations that need to be addressed to assure the validity of risk estimates derived using this protocol include:

- the array of samples collected for estimating airborne asbestos concentrations must be representative of the exposure environment;
- the time variation of airborne asbestos concentrations must be properly addressed;
- airborne samples must be collected on membrane filters that are suitable for preparation for analysis by transmission electron microscopy (TEM). Appropriate procedures for sample collection are described in Chatfield and Berman (1990) or the ISO Method (ISO 10312)[2];

[2]Note that the ISO Method (ISO 10312) is a refinement of the method originally published as the Interim Superfund Method (Chatfield and Berman 1990). It incorporates improved rules for evaluating fiber morphology. Both methods derive from a common development effort headed by Eric Chatfield.

- sample filters must be prepared for analysis using a direct transfer procedure (e.g., ISO 10312). Should indirect preparation be required (due, for example, to problems with overloading of sample filters), a sufficient number of paired samples will need to be collected and analyzed to establish a site-specific correlation between directly and indirectly prepared samples;

- samples must be analyzed by TEM;

- samples must be analyzed using the counting and characterization rules defined in ISO 10312 and the structures used to determine exposure concentrations for use with this protocol need to satisfy the dimensional criteria defined in Section 7.5 (i.e., structures longer than 10 μm and thinner than 0.4 μm). Importantly, ISO Method rules require separate enumeration and characterization of component fibers and bundles that are observed within more complex clusters and matrices. Such components, if they meet the dimensional criteria defined above must be included in the structure count;

- when risks are estimated using the risk tables (Tables 8-2 or 8-3) the risk values selected from the tables must be appropriate for the fiber type (i.e., chrysotile or amphibole) and the disease endpoint (i.e., lung cancer or mesothelioma) relevant to the situation of interest; and

- to use Tables 8-2 or 8-3, the concentration of total asbestos structures longer than 10 μm and thinner than 0.4 μm must be derived, divided by 0.0001, and multiplied by the risk estimate listed in the appropriate cell of the selected table to generate the risk estimate of interest.

Considerations that need to be addressed to assure the validity of risk estimates derived from soil or bulk measurements combined with release and transport modeling include:

- the array of samples collected for estimating source concentrations must be representative of the surface area or volume of source material from which asbestos is expected to be released and contribute to exposure;

- samples must be prepared and analyzed using the Modified Elutriator Method for soils and bulk materials (Berman and Kolk 1997, 2000), which is the only method capable of providing bulk measurements that can be related to risk;

- membrane filter samples prepared using the tumbler and vertical elutriator per the Superfund method must themselves be prepared for TEM analysis using a direct transfer procedure;

- TEM analysis must be conducted using the counting and characterization rules defined in the ISO Method (ISO 10312) in precisely the same manner that is described above for air measurements. Also, the same size categories need to be evaluated (in the same manner described above) to estimate exposures for use with this protocol to assess risk; and

- release and dispersion models that are selected for assessing risks must be appropriate to the exposure scenario and environmental conditions of interest. Such models must also be adapted properly so that they accept input estimates expressed in terms of fiber number concentrations. Procedures suggested for adapting such models are illustrated in a recent publication (Berman 2000).

Note, if new analytical procedures can be designed to focus on long structures, risks can be evaluated more cost-effectively. The alternate approach of spending a large proportion of available resources counting many (potentially non-potent or marginally potent) short structures, while not characterizing longer structures with adequate sensitivity or precision, leaves open the possibility of missing potentially serious hazards because a small population of extremely potent, long fibers were missed in a particular environment. Moreover, any potential contribution to risk by shorter structures will be incorporated to some extent by default, i.e., to the extent that similar proportions of such structures were also present in the environments from which the exposure-response coefficients were derived and such structures are known to have been ubiquitous in these environments (see, for example, Dement and Harris 1979; Gibbs and Hwang 1980; Hwang and Gibbs 1981).

8.3 RECOMMENDATIONS FOR FURTHER STUDY

A small number of limited and focused studies (described previously) are recommended in this document because they are likely to provide very cost-effective improvements to the quality of this document and may support substantial improvement to the recommended procedures for assessing asbestos-related risks. The recommended studies are:

(1) a focused study to expand our evaluation of the current U.S. EPA models to include other candidate models that might better track the exposure dependence of asbestos-related disease (Sections 7.2.2 and 7.3.2). Such models should also be used to explore and better represent the relationship between smoking and asbestos exposure (to the extent that data suitable for supporting such an analysis can be acquired); and

(2) a focused study to develop the supporting data needed to define adjustments for potency factors that will allow them to be used with an exposure index that even more closely captures asbestos characteristics that determine biological activity than the currently proposed index (Section 7.5).

Note that, by properly designing the second of the above-listed studies, it may also be possible to further address another outstanding issue that was previously identified: the question of whether exposure-response coefficients derived from mining studies are under-estimated relative to studies involving asbestos products because exposures in the mining studies may contain large numbers of non-asbestos particles contributed by the disturbance of host rock (Appendix D).

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